

1 **Online Supplemental Material to JAMA17-9394**
2 **Effect of More vs Less Frequent Follow-Up Testing on Total and Cancer-**
3 **Specific Mortality in Patients with Stage II-III Colorectal Cancer: The**
4 **COLOFOL Randomized Clinical Trial**

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31 **1. COLOFOL Study eProtocol** 32

33 **A pragmatic study to assess the frequency of surveillance tests after curative**
34 **resection in patients with stage II and III colorectal cancer**
35 – a randomised multicentre trial

36 —
37 Running title:
38 Assessment of frequency of surveillance after curative resection in
39 patients with stage II and III colorectal cancer.

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43 **Acronym: COLOFOL**
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46 by
47
48

49 *Peer Wille-Jørgensen, MD, Dr Med Sci.*
50 *Søren Laurberg, MD, Dr Med Sci*
51 *Henrik Toft Sørensen, MD, Dr Med Sci*
52 *Lars Pahlman, MD, Dr Med Sci*

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54 on behalf of the COLOFOL study group
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67 Correspondence to:
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69 Peer Wille-Jørgensen, M.D., Dr. Med. Sci.
70 Department of Surgical Gastroenterology K
71 H:S - Bispebjerg Hospital
72 DK-2400 Copenhagen NV
73 DENMARK
74 E- Mail: pwj01@bbh.hosp.dk
75

76 AIM

77

78 To conduct a prospective multicentre randomised study comparing total mortality, cancer-specific mortality,
79 recurrence-free survival, economic cost effectiveness, and quality of life (QOL) in patients having two
80 different schedules for follow-up after radical resection for colorectal cancer.

81

82

83 BACKGROUND

84

85 The value of follow-up programmes after radical surgery for colorectal cancer has been a con-
86 troversial issue for many years, and the scientific evidence supporting it remains sparse. Many
87 cohort and case-control studies have supported the effectiveness of follow-up (Rosen *et al.*, 1998)
88 (Figure 1 – lower case), but, until recently, randomised controlled trials have reported only
89 ambiguous findings regarding the efficacy of follow-up on mortality (Kievit & Bruinvels, 1995).
90 Nonetheless, despite the sparse evidence, follow-up programmes are being used in most clinics
91 treating colorectal cancer patients (Mella *et al.*, 1997).

92

93 The reasons for follow-up include:

- 94
- 95 • to obtain a better overall survival.
 - 96 • for scientific purposes
 - 97 • for psychological reasons

98

99 There is no doubt that the outcome of follow-up programmes can be considered from both efficacy
100 and cost perspectives (Kievit, 2002).

101

102 Recently, two systematic reviews with meta-analyses have been published investigating the same
103 five randomised controlled trials (Renéhan *et al.*, 2002; Jeffery *et al.*, 2002). The conclusions of
104 these reviews were the same: more intensive follow-up leads to lower mortality than sporadic or
105 less intensive follow-up. Subsequently, another randomised study was published confirming this
106 conclusion (Secco *et al.*, 2002). We have conducted a meta-analysis of all the randomised trials,
107 as shown in Figure 1 (upper case). We found a highly significant effect of more intensive follow-up
108 compared with less intensive follow-up (Peto Odds Ratio=0.62, 95% confidence interval:0.51-0.76,
109 $P < 0.001$).

110

111 However, these meta-analyses do create problems, mainly due to the heterogeneity in both the
112 intense and less intense follow-up regimens. The individual trials used different control modalities
113 and, in fact, the intensity of control in one study could be considered more aggressive than the
114 “intensive” group in other studies. The quality of the trials has also been questioned, as a high (and
115 probably not generalisable) number of local recurrences was seen in the two studies which showed
116 the highest effect of intensive follow-up (Secco *et al.*, 2002; Pietra *et al.*, 1998). The results of
117 these meta-analyses should, thus, be viewed with caution.

118

119 Further, the meta-analyses are not able to identify either which follow-up modality to use, or the
120 intensity (*i.e.*, investigation intervals) of the follow-up. Although some authors claim that we know
121 enough to make evidence-based recommendations (Smith & Bear, 1998) this claim is clearly
122 arguable – a point of view that is supported by the debate that followed Renéhan’s paper in *British*
123 *Medical Journal* in April 2002 (see www.bmjjournals.com/cgi/eletters/324/7341/813#23550)

124

125 Nonetheless, the published studies do imply that finding extraluminal recurrences (local recurrence
126 after rectal cancer and liver metastases after colorectal cancer) mainly causes the obtainable
127 benefit. The search for intraluminal recurrence does not alter the mortality. As the incidence of
128 local recurrence after rectal cancer is rapidly declining due to better surgical techniques and the
129 use of adjuvant treatment, the effect of looking for local recurrence after rectal cancer might be
130 limited. A subgroup analysis of three studies looking for liver metastases shows an effect on

131 survival in one of the meta-analyses (Figure 2) (Jeffery et al., 2002). Moreover, the preoperative
132 work-up for occult liver metastases was not routine when the referred trials where conducted.
133

134 In conclusion, the effectiveness of high-volume follow-up programmes after radical surgery for
135 colorectal cancer on overall survival is still not sufficiently elucidated to create evidence-based
136 guidelines. Despite this the Current Oncological Practice (COP) is moving towards high intensity
137 follow-up programmes (Figueiredo et al 2003, Worthington et al 2004, Anthony et al 2004). A
138 Minimal acceptable practice (MAP) might be just as good. It, thus, seems justified to perform a
139 randomised controlled trial randomising patients to high- or low-volume control programmes.
140

141

142 **Most used methods for control**

143

144 *Luminal recurrence:*

145 Endoscopy is the chosen method, but luminal recurrence is seldom and programmes looking for
146 luminal recurrence show no effect (Renahan et al., 2002)

147

148 *Local recurrence after rectal cancer:*

149 Endorectal ultrasound (US) has a high sensitivity and specificity (Löhnert et al., 2000), especially
150 when combined with guided biopsy (Hünerbein et al., 2001). MR-imaging (MRI) is perhaps even
151 more sensitive, but expensive (Pegios et al., 2002).

152

153 *Liver metastases:*

154 Average sensitivity for US is 55%, for CT 72%, MDCT 96% (Acta Rad. vol 46, no 1, feb. 2005, 9-
155 15), for MRI 76%, and for PET 90%. Of these, PET and MRI are not generally available.

156

157 *General recurrence:*

158 PET is probably the most sensitive of detecting disseminated disease Monitoring of
159 carcinoembryonic antigen (CEA) remains controversial (Lennon et al., 1994), but might be justified,
160 if related to perioperative measurements (Renahan et al., 2002; Li Destri et al., 1998).

161

162 **STUDY PROCEDURES**

163

164 *Recruitment and Eligibility*

165 Centres will be recruited from all over Scandinavia, the UK, Poland, Hungary, Uruguay and
166 Holland. At each participating centre, consecutive patients receiving radical surgery for colorectal
167 cancer (emergency or elective) will be considered for inclusion. Those who are ineligible or who
168 refuse consent will be followed in an observational follow-up design.

169

170 Inclusion criteria:

- 171
- 172 • Radical elective or emergency surgery (R0-resection) for colorectal adenocarcinoma –
173 with or without adjuvant treatment, and
 - 174 • Age \leq 75 years, and
 - 175 • Provision of written informed consent for participation, and
 - 176 • “Clean colon” verified by perioperative barium enema or colonoscopy last 3 months
177 post-surgery, and
 - 178 • Tumour stage:II-III (T_{any} N₁₋₂ M₀, T₃₋₄N_{any}M₀, Dukes' B - C) as staged at the pretreatment
179 staging procedure (clinical staging)

180

181 Pre- or postoperative chemotherapy and/or radiation therapy is allowed.

188
189 **Exclusion criteria:**

- 190
- 191 • A clinical diagnosis of HNPCC (non hereditary polyposis colorectal cancer) or FAP
(familial polyposis coli),
 - 192 • Local resection for colorectal cancer (e.g., TEM-procedure),
 - 193 • Life-expectancy less than 2 years due to concurrent disease (e.g., cardiac disease,
terminal multiple sclerosis, liver cirrhosis),
 - 194 • Inability to provide informed consent or refusal to do so,
 - 195 • Inability to comply with the control or intense follow-up programme,
 - 196 • Participation in other clinical trials interfering with the control-programmes
 - 197 • Other or previous malignancies (except for non-melanoma skin cancer)

200

201 Informed consent (written) is obtained within 30 days after the primary tumour classification has
202 been obtained. Patients refusing to participate should be asked for consent to be followed in the
203 cohort, using data on their actual control-programme and their clinical course.

204
205 **Randomisation and treatments**

206 Randomisation will take place by Internet from a central randomisation unit (appendix 12) placed at
207 Department of Clinical Epidemiology in Århus Denmark. Randomisation will be stratified according
208 to tumour stage and clinical centre. Randomisation will be blocked in variable groups of which the
209 size will be kept secret for the participating centres. The allocation procedure should be concealed
210 to the deliverers of treatment.

211
212 **Study Follow-up Regimens**

213 CEA will (if possible) be measured on all colorectal cancer patients before surgery or preoperative
214 adjuvant therapy, and one month after the completion of primary treatment. All patients should
215 have "clean colon" within 3 months perioperatively, and at least one imaging procedure
216 (Ultrasound, MRI, or CT) of the liver and X-ray of the lungs perioperatively. In both groups, an
217 unlimited number of endoscopies are allowed. Interval diagnostic evaluation will be allowed for all
218 subjects presenting symptoms.

219 A clinical visit 4-6 weeks after operation is recommended for information and allocation.

220
221 *1: Low frequency follow-up regimen*

- 222
- 223 • CEA preoperatively and one month postoperatively – a missing preoperative CEA is not
considered an exclusion criteria, and will be handled as missing data.
 - 224 • CEA, multislice CT/ or MRI of the liver and X-ray/CT of the lungs 12 and 36 month after
surgery. Patients are instructed to contact their reference centre if symptoms of
recurrence occur.
 - 225 • If recurrent disease is suspected, a standardised work-up for diagnosis and treatment
will be applied (appendix 2-3)

226
227 *2: High frequency follow-up regimen*

- 228
- 229 • CEA preoperatively and one month postoperatively – a missing preoperative CEA is not
considered an exclusion criteria, and will be handled as missing data.
 - 230 • CEA, multislice hepatic CT, or MRI and X-ray or CT of the lungs at 6, 12, 18, 24, and 36
months. Patients are instructed to contact their reference centre if they experience any
symptoms of recurrence.

- 244 • If recurrent disease is suspected, a standardised work-up for diagnosis and treatment
245 will be applied (appendix 2-3)

248 Patients with newly elevated CEA in whom recurrence cannot be found at other investigations
249 could be sent for PET-scanning (if available). If this does not disclose metastatic disease, it should
250 be repeated after 3 months (if the CEA is still elevated). For algorithm see appendix 2.

251 At each follow-up visit, a blood sample is taken for storage (-80°) for possible later analyses for
253 prognostic or diagnostic factors.

254 In both groups, an unlimited number of endoscopies are allowed, but should be performed after the
256 same schedule in each randomisation-group two groups. The same goes for CT/MRI/US of the
257 pelvis for recurrence after rectal cancer. The local programmes in this respect should be registered
258 centrally, and divergations from this programme should be registered in the CRF. Interval control
259 should be performed in case of symptoms, and the procedures used should be according to the
260 guidelines in appendix 2. These interval controls should be registered on the CRF.
261 It is allowed to call patients for extra clinical follow- up after 48 and 60 months, as long as the
262 programme is even in the two randomisation arms.

263 **Quality of examinations**

264 Before entering a trial, the individual centre should prove the high quality of their control-
266 examinations. The central steering group's diagnostic board should approve five consecutive
267 examples. Guidelines for examinations are listed in Appendix 1.

270 **Patient treatment if recurrence**

272 If recurrence is suspected or verified, the patient-case should be evaluated in a local (country- or
273 county separated) MDT conference, in order to decide and offer the best available treatment for
274 the patient (salvage surgery, palliative chemotherapy and/or radiotherapy, no treatment). These
275 groups also form the local steering-groups for the study. They should preferably include a surgeon,
276 a radiologist, and an oncologist.

277 An algorithm for treatment of recurrence is found in Appendix 3.

281 **Efficacy parametres**

283 The primary effect-parameter of the study will be total mortality and cancer-specific mortality after 5
284 years; the secondary endpoint will be time to diagnosis of recurrence (*i.e.*, recurrence-free
285 survival).

288 **Data collection**

290 In order to track all potentially eligible patients, a system for reporting all patients diagnosed with
291 colorectal adenocarcinoma in the pathological departments of participating hospitals should be in
292 place at each participating centre. All patients having radical surgery and who fulfil the inclusion
293 criteria are to be reported to the secretariat. The reason for not including individual patients is to be
294 reported. Case-record forms (CRF) (Appendix 6) for individual patients are to be filled in at the
295 individual centres. Reports should be collected centrally after every planned or non-planned
296 control. All registrations (CRF) are communicated centrally by means of an internet-based
297 database with the central server placed at The Department of Clinical Epidemiology in Århus,
298 Denmark after each visit (appendix 12).

299
300 Patients refusing to participate should be followed according to the individual departments' local
301 guidelines. Each control-visit among patients in this group should be reported, if consent for
302 observational follow-up is obtained.

303
304 If economically possible, each centre will receive a monitoring visit at least once a year.

305
306 The following data will be obtained on all randomised subjects and those who give consent for
307 observational study:

- 308 • Baseline demographic, clinical, and lifestyle factors (date of birth, major chronic
309 illnesses, smoking, alcohol intake, medications, etc);
310 • Results of all diagnostic evaluations for metastatic disease during the initial evaluation;
311 • Description of initial surgical, adjuvant, and radiation treatment;
312 • Postoperative final staging
313 • Findings from all cancer surveillance tests obtained after diagnosis;
314 • Detailed description of all cancer treatment applied after randomisation;
315 • Quality of life (QOL) assessment by telephone interview at 1, 3, and 5 years after
316 randomisation. A standardised and evaluated QOL-instrument that takes follow-up
317 regimens into consideration will be used. (See Appendix 3.)

319 320 321 **Statistical analysis and power**

322 Results will be evaluated both on an intention-to-treat basis and on an as-treated (per protocol)
323 basis. Patients who withdraw their informed consent and, thus, change their control-programme
324 remain in their allocation group when evaluated on the intention-to-treat basis, and are excluded
325 when evaluated on the fulfilled protocol basis. Non-randomised patients and patients withdrawing
326 their informed consent will be analysed separately.

327
328 On the basis of the results listed in Figure 1, an estimate of 5 years' mortality at 60% and a
329 MIREDIF (Minimal Relevant Difference) of 6% seem justified. With a risk of type 1 error at 5% and
330 type 2 error of 15%, about 1,100 patients should be randomised to each group. With an expected
331 dropout rate of about 20%, the planned number of randomised patients should be 2,500.

332
333 Survival data will be analysed according to the Kaplan-Meier method and comparison between
334 groups will be performed with the log-rank method. Binomial data will be analysed with Chi-
335 square statistics and continuous data with Mann-Whitney U test.

336
337 No interim analyses are planned, as this would stop inclusion for several years.

338
339 Level of significance two-sided $p < 0.05$.

340 341 342 **Ethical considerations**

343 The meta-analyses provide no reason for a firm conclusion on the effectiveness of specific follow-
344 up programmes, although arguably the studies "consistently" suggest that more follow-up (of some
345 sort) is better than no follow-up at all. The question is how often patients have to be checked.
346 Community equipoise exists due to the uncertainty of the regimens. There might be problems with
347 patients' and doctors' equipoise, as patients report a strong preference for pre-scheduled follow-up
348 (Stigglebout *et al.*, 1997), but the opposite feelings also exist among patients. In a similar
349 investigation among patients with breast cancer, 66.5% of the women accepted randomisation into
350 follow-up in the primary or hospital sector.

351
352
353

354 Patients in the intervention group might appear to be offered more intense treatment. It is doubtful
355 whether this is of benefit for the individual patient, considering the psychological stress the
356 intensive follow-up programme and the possible side effects of extra therapy will imply for the
357 patient.

358
359 Patients refusing to participate will be followed according to the individual departments' local
360 guidelines. Patients who refuse to participate are followed in the database. Consent for this is not
361 needed, as this is a part of the general record keeping.

362
363 All participants must give informed consent for participation. This can be withdrawn at any time.

364
365 The demands in the Declaration of Helsinki are met.

366 367 368 **Organisation**

369
370 The study will be undertaken under the auspices of a steering committee elected among the
371 persons in the study group. The steering group should consist of preferable 2 persons from each
372 participating country. The monitoring groups will be appointed among people not directly involved
373 in the investigation.

374
375 Centres will be recruited from all over Denmark, Sweden, Poland and Uruguay. Due to the
376 patients' preference for pre-scheduled follow-up, a low recruitment rate can be expected. Each
377 centre should be able to recruit at least 50 patients within two years. This requires at least 50
378 participating centres.

379
380 Each centre will appoint a principal investigator who will be responsible for local administration and
381 recruitment of diagnostic departments (Radiology, Nuclear Medicine, Ultrasound departments).
382 Each country appoints a monitoring committee, and a committee for evaluation of patients
383 suspected of recurrence. Each centre is recommended to appoint a study nurse for running the
384 study.

385
386 A central secretariat will be placed in a suitable institution (pt at Cochrane Colorectal Cancer Group
387 at Bispebjerg Hospital, Copenhagen, Denmark) and is staffed with a full-time secretary and
388 preferably with a half-time academic employee. The secretariat will collect a log of all included
389 patients, monitor the individual centres for inclusion of eligible patients on a daily basis, and serve
390 as the central allocation unit. If a centre does not recruit at least 30% of eligible patients, the centre
391 should be withdrawn from the study.

392 393 394 **Economics**

395
396 No industrial sponsors can be expected to volunteer in this project. Funds will be sought from
397 private and official funds in the participating countries. Funds from the EU will also be considered.
398 The central steering group will support applications for local support.

399
400 If economically feasible each included patient should be reimbursed with 125 EUROs to be given
401 to the individual department. Total expense is estimated to be 375,000 EUROs.

402
403 Centres will cover their own expenses for the diagnostic tests.

404
405 Organisational expenses are also expected for the secretariat and data handling unit (estimated at
406 100,000 EUROs/year), for travel and meeting expenses, for local monitoring and secondary
407 treatment groups (estimated at 150,000 EUROs/the whole study). Expenses for the diagnostic
408 investigations and study-nurses in the individual centres are to be met directly by the centres. With

409 2 years of recruitment and 5 years of follow-up, the total requirement for funds will be about
410 1,250,000 EUROS.

411
412 The Nordic Cancer Union was sought for grants for starting and detailed planning of the study by
413 May 15, 2003; 25.000 EUROS were allowed to cover the planning phase and a feasibility pilot
414 study.

415
416 The Danish Cancer Society has granted 800.000 dkr. for use in 2007/2008. And the Danish
417 Agency for Science, Technology and Innovation donated 1.082.550 dkr. to be used in 2008-2010.

418 419 **Side-protocols**

420 Such are allowed in the respect that they do not interfere with the main project. At this stage, the
421 following side-protocols are planned:

- 422
423 • Cost effectiveness-analyses stratified for each participating country;
424 • Sampling of blood and tissue for risk-factor analysis;
425 • Quality of life for included patients
426 • Observational study of survival and risk factors after salvage surgery for recurrence.

427 Private companies might be involved in some local side-protocols. This could create conflict of
428 interests. Local projects on COLOFOL patients will be performed with no responsibility from the
429 steering group, but will have to be approved by the steering group, ensuring no interference with
430 the main project occurs. The side-protocols have to develop their own patient information and
431 ethical considerations.

432 433 **Time schedule**

434
435 2003-4: Planning, fund-raising, final protocol, case record forms, ethical committees, recruitment
436 of centres, feasibility studies.
437 2005-8: Inclusion of patients
438 2013: Last patient followed-up for 5 years.

439 440 **Publication**

441 The Steering Group will appoint a writing committee to report the results on behalf of the
442 COLOFOL-group. All investigators will be eligible. All investigators will be listed by name at the end
443 of the presenting paper.

444 445 **Amendments to the original protocol decided by the steering group after initiation of trial:**

446 Regarding **Data collection:**

447 The initial request of the reporting of all non-included eligible patients proved difficult to insure in all
448 participating centers, so a comparison of study and source population will be explored in a
449 separate paper.

450
451 The Quality of life measurement will be conducted as a side protocol and reported as a separate
452 paper.

453
454 The Cost effectiveness will be reported as a separate paper.

464 Regarding **Efficacy parameters**:

465
466 As evidence suggested that the 3 year effect-parameter of total mortality and cancer-specific
467 mortality to be an excellent surrogate to 5 years, the steering decided in September 2012 to
468 publish both 3 and 5 years total mortality and cancer-specific mortality, along with the secondary
469 endpoint of recurrence-free survival.

470
471 Regarding **Organisation**:

472 The initial requirement that If a centre does not recruit at least 30% of eligible patients, the centre
473 should be withdrawn from the study and that each centre should be able to recruit at least 50
474 patients within two years, were explicitly based on at least 50 participating centres. Despite
475 continues effort neither the UK, Holland nor Hungary will be participating, so an adjustment is
476 needed to achieve the planned number of randomised patients. The Steering Group decided in
477 September 2010 to impose cut-off >20 included patients to insure quality of the management at
478 the participating department in Denmark, Ireland, Poland, Sweden and Uruguay.

479
480
481 Regarding **Time schedule**:

482 The schedule will adjusted according to the prolonged inclusion period, so that inclusion are to be
483 completed by the end of 2010 and the completion of the last patient follow-up for 5 years by the
484 end 2015/early 2016.

485
486
487
488 **Appendices**

- 489
490 1. Recommended techniques for diagnostic investigations and certification
491 2. Algorithm for positive findings in the follow-up
492 3. Guidelines for handling of detected recurrences in the study groups
493 4. QOL-instrument
494 5. Participating Centres and persons
495 6. Registration forms
496 7. Steering group
497 8. Monitoring committee (to be elected in autumn 2004)
498 9. Patient information and lay person protocol (In local languages)
499 10. Databases and randomisation procedures
500 11. Approval from ethical committees
501 12. Flow-chart and inclusion chart

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571 **Figure 1**

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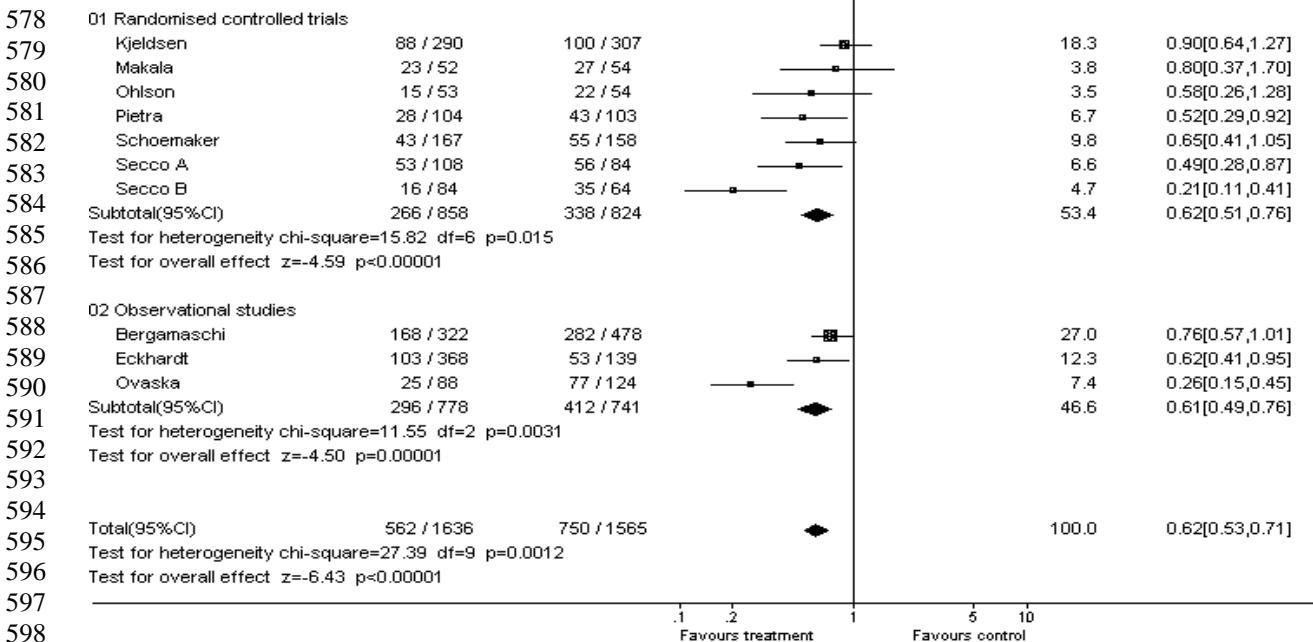
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.1 .2 1 Favour treatment Favour control

597 **Figure 2**

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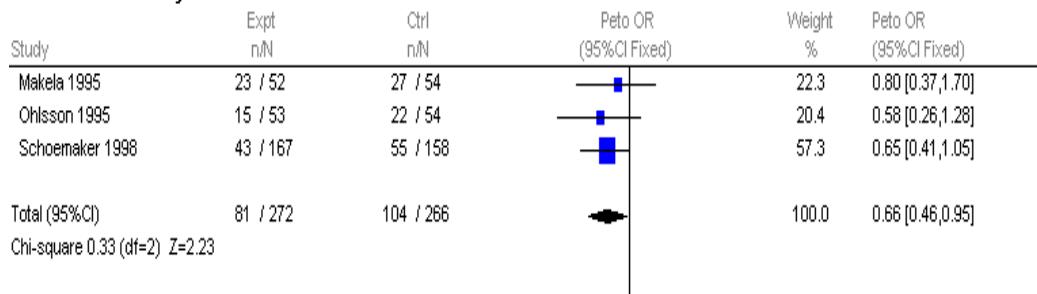
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606 Comparison: Liver imaging versus no liver imaging

607 Outcome: Mortality



624 APPENDIX 1.

625
626 GUIDELINES FOR NEWCOMERS TO THE COLOFOL STUDY GROUP.

627
628
629 The COLOFOL STUDY GROUP is open to new local investigators. Inclusion of patients in the
630 study will go on until the end of 2008.

631
632
633 Do you want to join the COLOFOL STUDY GROUP? Then this is what you should do:

- 634
635
636
637
638 1. Make CT scans according to the guidelines in appendix 1B-1D.
639
640
641 2. Fill in the Radiological CT protocol questionnaire (appendix 1E) and send the CTs and the
642 questionnaire to Lennart Blomqvist or Dennis Tønner Nielsen.
643
644
645 3. Fill in the department registration form (appendix 1F) and send it to

646
647 COLOFOL
648 C/o Peer Wille-Jørgensen
649 Department of Surgery K
650 Bispebjerg Hospital
651 Bispebjerg Bakke 23
652 2400 København NV

653
654
655
656 When your CT scans have been approved, you will receive a login and a password to the
657 COLOFOL database.

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679
680 **Appendix 1 A**
681

682 **COLOFOL**
683

684 **Common side protocol**
685 **Bank of blood and tissue samples**

686
687 **Blood samples**

688 Three samples of 10 ml peripheral blood are collected preoperatively prior to any neoadjuvant
689 chemotherapy and/or radiotherapy. 10 ml is drawn in one EDTA tube, 10 ml in one heparinized
690 tube, and 10 ml in one serum tube.

691 Samples are spun for 15 minutes at 1500G within 30 minutes after collection.

692 The spun EDTA tube and the spun heparinized tube samples are split into 10 fractions: 3 x
693 1.6 ml plasma, 1 x 1.6 ml buffy coat, and 1 x 1.6 ml erythrocyte fraction.

694 The spun plasma tube sample is split into 3 x 1.6 ml. Altogether 13 fractions collected in
695 cryotubes are present after the separation.

696 The 13 cryotubes are immediately frozen at -80°C until analysis.

700
701
702 **Tissue samples**

703 If possible due to the tumour size, four biopsies each measuring appr. 0.5 x 0.5 x 0.5 cm are cut
704 from the fresh, unfixed tumour immediately after the specimen has been resected. The biopsies
705 are stored in cryotubes marked T1, T2, T3, T4 (tumour).

706 A biopsy of at least 0.5 x 0.5 cm is cut from the macroscopically normal mucosa appr. 10 cm from
707 the tumour. The normal biopsy is put in a cryotube marked N (normal).

708 All tissue samples should be snapfrozen, and stored at -80°C until analysis.

709
710
711 **Storage**

712 Blood and serum samples are stored at each investigational center until analysis.

713 As a general agreement, all samples are available for COLOFOL research projects after approval
714 of the COLOFOL Steering group.

716 APPENDIX 1 B

717 COLOFOL

719

720

721

722 Guidelines

723

724 Liver CT

725

726 Patient position: Supine

727 Oral contrast material: Water

728 Breath-hold: One single breath-hold in each phase in maximum inspiration

729

730 The values in the protocol are recommended parameters.

731

732

733

734 PROTOCOL

735

736

PROTOCOL	BEFORE CONTRAST	AFTER CONTRAST		
		SINGLE-SLICE	4 - SLICE	16 - SLICE
SCAN COVERAGE	liver	liver	liver	liver
COLLIMATION		5mm	4x2,5	16x1,5
PITCH			1,25	1,5
ROTATION TIME (sec)		1	0.75	0.75
kV	same parameters as after contrast	130	120	120
mAs		180	180	200
Matrix min/filter		512/B	512/B	512/B
IV-kontrast				
Concentration		300 mg I / ml	300 mg I / ml	300 mg I / ml
Volume		2 ml / kg (max 180 ml)	2 ml / kg (max 180 ml)	2 ml / kg (max 180 ml)
Flow		4 ml/sec	4 ml/sec	4 ml/sec
Scan delay		50 sec	65 sec	70 sec
Preparation	2 glasses of water	2 glasses of water	2 glasses of water	2 glasses of water

737

738

739 Post-processing

740

741

742

743 The images should be evaluated with different W/L settings. Especially specific liver window settings are recommended for evaluation.

744

745 After the baseline scanning all parameters have to be constant in subsequent control
746 examinations.

747

748

749

750

751 APPENDIX 1 C

752 COLOFOL

755 Guidelines

756 Liver and abdominal CT

761 Patient position: Supine

762 Oral contrast material: Barium – or iodic contrast material (abdomen) and water (liver)

763 Breath-hold: One single breath-hold in each phase in maximum inspiration

764

765 The values in the protocol are recommended parameters.

766 PROTOCOL

769

770

PROTOCOL	BEFORE CONTRAST	AFTER CONTRAST		
		SINGLE-SLICE	4 - SLICE	16 - SLICE
SCAN COVERAGE	liver	Liver + abdomen	Liver + abdomen	Liver + abdomen
COLLIMATION		5mm	4x2,5	16x1,5
PITCH			1,25	1,5
ROTATION TIME (sec)		1	0,75	0,75
kV	same parameters as after contrast	130	120	120
mAs		180	180	200
Matrix/filter		512/B	512/B	512/B
IV-kontrast				
Concentration		300 mg I / ml	300 mg I / ml	300 mg I / ml
Volume		2 ml / kg (max 180 ml)	2 ml / kg (max 180 ml)	2 ml / kg (max 180 ml)
Flow		4 ml/sec	4 ml/sec	4 ml/sec
Scan delay		50 sec	65 sec	70 sec
Preparation	2 glasses of water	2 glasses of water	2 glasses of water	2 glasses of water

771

772

773 Post-processing

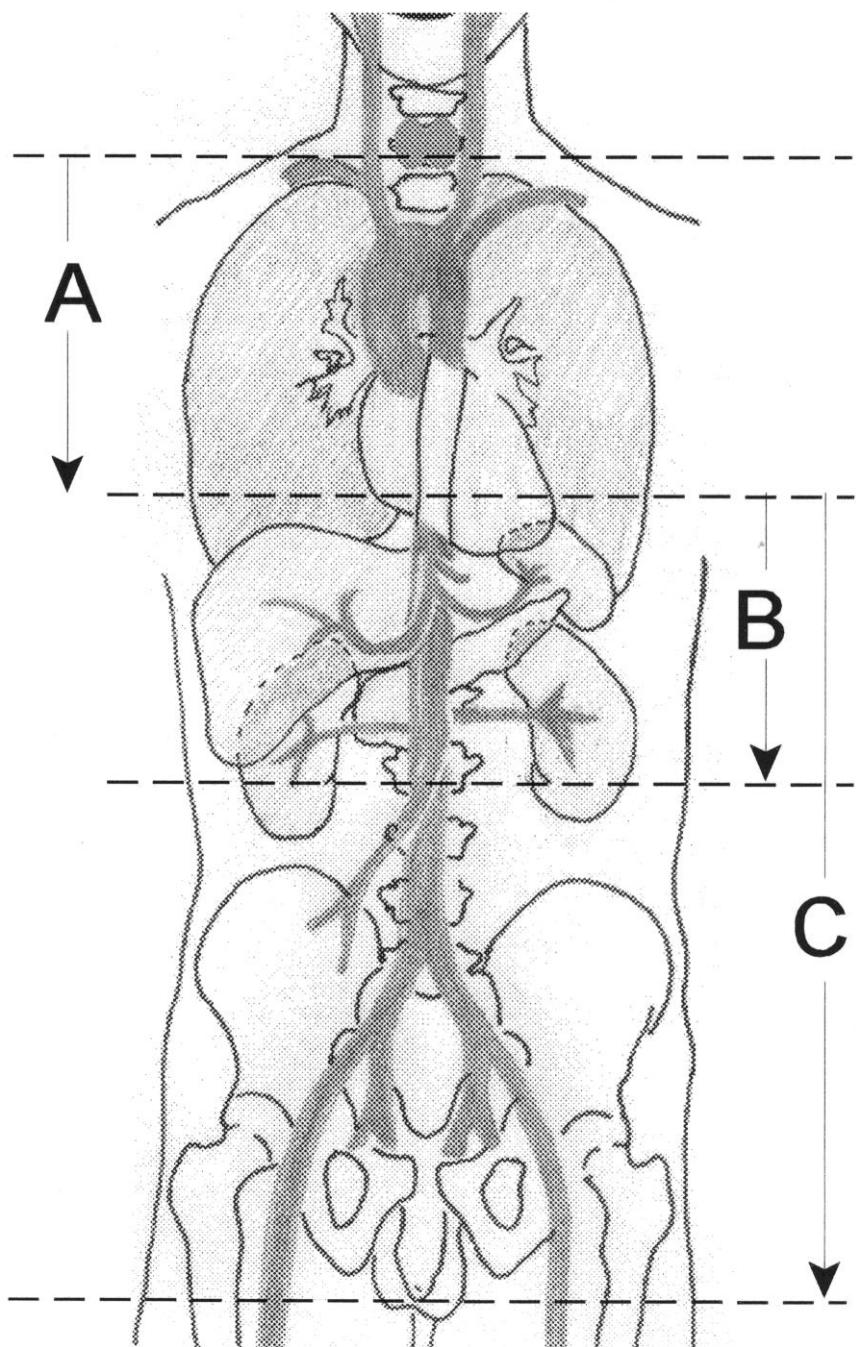
774

775 The images should be evaluated with different W/L settings. Especially specific liver window
776 settings are recommended for evaluation.

777

778 After the baseline scanning all parameters have to be constant in subsequent control
779 examinations.

780



781

782

783

784

785

786 **A = Thorax**

787 **B = Liver**

788 **C = Liver/abdomen**

789 **APPENDIX 1 D**

790 **COLOFOL**

792

793 **Guidelines**

794

795 **CT-Chest – low dose**

796

797

798

799 Patient position: Supine
800 Oral contrast material: -
801 Breath-hold: One single breath-hold in each phase in maximum inspiration

802

803 The values in the protocol are recommended parameters.

804

805

806 **PROTOCOL**

807

808

	Single slice	4-slice
Scan coverage:	Thorax	Thorax
Increment	5 mm	3.2 mm
Collimation	5 mm	4 x 5 mm
Pitch	1.5	1.75
Rotation time	1.0	0.75 sec.
KV	130	120
mAs	65	40
Matrix/filter	512/B	512/B
IV contrast		-
Concentration		-
Volume		-
Scan delay		-

809

810

811

812 After the baseline scanning all parameters have to be constant in subsequent control
813 examinations.

814

815

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823 **APPENDIX 1E**
824
825 **COLOFOL RADIOLOGICAL CT PROTOCOL QUESTIONNAIRE**
826
827 **Hospital:**..... **Address:**.....
828
829 **Surgeon**..... **Address:**.....
830
831 **Radiologist:**..... **E-mail:**.....
832
833
834 **Technologist:**..... **Email:**.....
835
836 **Phone:**..... **Fax:**.....
837
838
839 **Equipment 1 (manufacturer/name/year):**..... /..... /.....
840
841 **Number of detectors:**.....
842
843
844 **Equipment 2 (manufacturer/name/year):**..... /..... /.....
845
846 **Number of detectors:**.....
847
848
849
850 **Equipment 3 (manufacturer/name/year):**..... /..... /.....
851
852 **Number of detectors:**.....
853
854
855 This questionnaire (three pages) is sent to (for Sweden):
856
857 Lennart Blomqvist M.D. Ph.D.
858 ADR Centrala röntgen
859 Karolinska Universitetssjukhuset Solna
860 171 76 Stockholm
861 Phone: 0046-8-51776117
862
863 (For Denmark and Poland)
864 Dennis Tønner Nielsen, Overlæge
865 Radiologisk afd. R
866 Århus Universitetshospital
867 Århus Sygehus
868 Nørrebrogade 44
869 8000 Århus
870 Denmark
871
872 For correspondence use also: lennart.blomqvist@kirurgi.ki.se or dtnie@as.aaa.dk
873
874 After receiving the questionnaire, the corresponding site (surgeon/radiologist/technologist) will
875 receive a confirming e-mail.
876

877 COLOFOL

878

879 **Liver CT** **RADIOLOGICAL PROTOCOL QUESTIONNAIRE**

880

881 **Patient position:**.....

882

883 **Oral contrast material:**.....

884

885 **Breath-hold:**.....

886

PROTOCOL	BEFORE CONTRAST	AFTER CONTRAST		
		Equipment 1	Equipment 2	Equipment 3
SCAN COVERAGE	liver	liver	liver	liver
COLLIMATION				
PITCH				
ROTATION TIME (sec)				
KV				
Mas				
Matrix min/filter				
IV-contrast				
Concentration				
Volume				
Flow				
Scan delay				
Preparation				

887

888 **Liver and Abdominal CT**

889

890 **Patient position:**.....

891

892 **Oral contrast material:**.....

893

894 **Breath-hold:**.....

895

PROTOCOL	BEFORE CONTRAST	AFTER CONTRAST		
		Equipment 1	Equipment 2	Equipment 3
SCAN COVERAGE	liver	liver	liver	liver
COLLIMATION				
PITCH				
ROTATION TIME (sec)				
KV				
Mas				
Matrix min/filter				
IV-contrast				
Concentration				
Volume				
Flow				
Scan delay				
Preparation				

896

897

898

899	COLOFOL		
900	CT THORAX	RADIOLOGICAL PROTOCOL QUESTIONNAIRE	
901	Patient position:	
902	Oral contrast material: -	
903	Breath-hold:	
904			
905			
906			
907			
908			
909			
910			
911			
912	PROTOCOL		
913			
914			
	Equipment 1	Equipment 2	Equipment 3
Scan coverage:			
Increment			
Collimation			
Pitch			
Rotation time			
KV			
MAs			
Matrix/filter			
IV contrast		-	
Concentration		-	
Volume		-	
Scan delay		-	
915			
916			
917	Image storing	PACS	†
918			
919		Optical discs	†
920			
921		DVD/CD	†
922			
923		Film	†
924			
925			
926	General comments:		
927			
928			

929 APPENDIX 1F
930
931
932
933

934 **REGISTRATION AS PARCIPATING DEPARTMENT IN COLOFOL**
935
936

937 Department:.....
938
939 Address.....
940
941

942 Country:.....
943
944 Name of local responsible investigator:.....
945
946 E-mail:.....
947
948 Fax:.....
949
950 Telephone:+.....
951
952
953

954 **Departments protocol ID:.....(to be filled out by COLOFOL secretariat)**
955
956

957 In order to participate in the COLOFOL study, you will have to fulfill following demands:
958
959

960 1.The National Ethical Comittee has accepted the protocol: Yes.... No.... Waiting.....
961
962

963 2. I have read the full protocol and it´s appendices: Yes.... No....
964
965

966 3. According to the protocol, I agree to:
967

968 a) include at least 50 patients during the study period, Yes.... No.....
969
970 b) include at least 30% of eligible patients Yes.... No

971 c) report on all included patients and their follow-up Yes No

972 d) report on all patients that fullfill the inclusion criteria Yes.... No.....
973 eventhough they're hit by an exclusion criteria
974
975

976 e) inform the primary referring doctor about the project Yes.... No.....
977
978 f) inform the patient of his/her paticipation Yes No.....
979
980

981 4. I have made contracts with the local radiology department in
982 order to have the planned investigations performed. Yes.... No.... Waiting.....
983
984

989
 990
 991 5. Participating in a local multidisciplinary team in order to treat
 992 recurrences: Yes.... No.... Waiting.....
 993
 994
 995 a) Name of oncology department:.....
 996
 997 b) Name of Liver surgery department.....
 998
 999 c) Name of Thoracic surgery department.....
 1000
 1001
 1002
 1003
 1004 6. Being able to withhold local oncology departments from interfering
 1005 with the COLOFOL-protocol. This means no extra investigations for
 1006 recurrence unless symptoms Yes..... No.....
 1007
 1008
 1009 7. I agree not to present any follow-up results of the allocated patients
 1010 in the COLOFOL-study, orally and written, prior to the presentation
 1011 of the COLOFOL-study. Yes.... No....
 1012
 1013
 1014 8: Being able to inform the primary referring doctor of the project: Yes... No....
 1015
 1016
 1017 9. Being able to inform the patient of his/her participation: Yes.... No....
 1018
 1019
 1020 10.
 1021 Signature by the local responsible investigator
 1022
 1023
 1024 Send this form to:
 1025 COLOFOL
 1026 c/o Peer Wille-Jørgensen
 1027 Department of Surgery K
 1028 Bispebjerg Hospital
 1029 DK-2400 Copenhagen NV
 1030 DENMARK
 1031 Send CT-scans and CT questionnaire (see app. 1b-e) to:
 1032
 1033 Sweden and Uruguay:
 1034 Denmark and Poland
 1035 Lennart Blomqvist
 1036 Dennis Tønner Nielsen
 1037 ADR Centrala röntgen
 1038 Radiologisk afd. R
 1039 Karolinska Universitetssjukhuset Solna
 1040 Århus Universitetshospital
 1041 171 76 Stockholm
 1042 Nørrebrogade 44
 1043 Sweden
 1044 8000 Århus
 1045 Denmark
 1046
 1047 **For the COLOFOL secretariate exclusively:**
 1048
 1044 **Liver scans approved:** Yes.... No.....
 1045
 1046
 1047 **Department included:** Yes.... No.....
 1048

1049 **Appendix 2**

1050
1051 **Algorithm for positive findings in follow-up of CRC according**
1052 **to the COLOFOL-protocol**

1053
1054
1055 **I. Serial CEA-measurements in follow-up of CRC**

- 1056
1057 • CEA is tested 1 month postoperatively, for an individual baseline value.
1058
1059 • In further testing, the cut off level is defined as 5 pg/ml in individuals with baseline CEA levels < 5,
1060 while in individuals with baseline CEA levels >= 5, the cut off level is defined as 30% above baseline
1061 value.
1062
1063 • Further on CEA is tested at 12 and 36 months in the low frequency group and at 6, 12, 18, 24 and 36
1064 months in the high frequency group, as part of the testpackage

1065
1066
1067
1068 **Algorithm for handling of CEA test results with negative scheduled CT-scan and negative CXR:**

- 1069
1070 1. If scheduled test is
1071 1.1. < 5 pg/ml in patients with base line value < 5, or
1072 1.2. < 30% above base line in patients with baseline value > 5.
1073
1074 Patient will be followed as scheduled, according to protocol
1075
1076
1077
1078 2. If scheduled test is
1079 2.1. >= 5 pg/ml, but < 10 pg/ml in patients with base line value < 5 or
1080 2.2. >= 30% above base line but < 100% above base line in patients with base line value > 5
1081
1082 A new test will be performed after 4 weeks.
1083
1084 2.3. If this test shows a further increase, the test is regarded positive (see section II).
1085 2.4. If not, a new test will be performed after 4 weeks*
1086
1087
1088 3. If scheduled test is
1089 3.1. >= 10 ng/ml, in patients with base line value < 5, or
1090 3.2. >= 100 % above base line value in patients with base line value > 5
1091
1092 A new test will be performed immediately.
1093
1094 3.3. If this test verifies the increase in CEA level, the test is regarded positive (see section II).
1095 3.4. If not, a new test will be performed after 4 weeks*

1096
1097 * The result will be handled according to the same principles as above for scheduled tests.

1107 **II Algorithm for positive findings in follow-up**

1108 **1. Positive CEA test and negative scheduled abdominal CT**

1111 1.1. CT thorax + MRI abdomen + pelvis and rigid sigmoidoscopy in rectal cancer

1113 1.1.1. Positive finding: Evaluation in regional multidisciplinary board*

1114 1.1.2. Negative finding (of complementary examinations): Evaluation in regional
1115 multidisciplinary board*. Options are: diagnostic laparoscopy, contrast enhanced
1116 ultrasonography, PET (if available) or new CT thorax + MRI of abdomen/CT in right
1117 side colon cancer (+ pelvis and sigmoidoscopy in rectal cancer) after 6 weeks

1119 **2. Positive finding on scheduled CT thorax, abdomen or CXR (+/- positive CEA)**

1122 2.1. CT thorax + MRI abdomen + pelvis and rigid sigmoidoscopy in rectal cancer

1124 2.1.1. Positive finding: evaluation in regional multidisciplinary board*

1125 2.1.2. Negative finding (of complementary examinations) with positive CEA; Evaluation in
1126 regional multidisciplinary board*. Options are: diagnostic laparoscopy, contrast enhanced
1127 ultrasonography, PET (if available) or new CT thorax + MRI of abdomen/CT in right
1128 side colon cancer (+ pelvis and sigmoidoscopy in rectal cancer) after 6 weeks

1129 2.1.3. Negative finding (of complementary examinations) with negative CEA; follow-up
1130 according to protocol

1132 **III Algorithm for positive findings in symptomatic patients**

1136 **1. "Malignant symptoms" or positive finding on any imaging for any reason**

1138 1.1. CEA + CT thorax and MRI of abdomen + pelvis and rigid sigmoidoscopy in rectal cancer

1140 1.1.1. Positive finding: evaluation in regional multidisciplinary board*

1141 1.1.2. Negative finding (of complementary examinations) with positive CEA; Evaluation in
1142 regional multidisciplinary board*. Options are: diagnostic laparoscopy, contrast
1143 enhanced ultrasonography, MRI of abdomen/CT in right side colon cancer + pelvis
1144 and sigmoidoscopy in rectal cancer, PET (if available) or new CT thorax after 6 weeks

1145 1.1.3. Negative finding (of complementary examinations) with negative CEA; follow-up
1146 according to protocol

1147 **2. Bleeding per an**

1148 2.1. Sigmoidoscopy if rectal cancer; colonoscopy if colonic cancer

1153 2.1.1. Positive finding: CT thorax + MRI of abdomen/CT in right side colon cancer + pelvis
1154 in rectal cancer and evaluation in regional multidisciplinary board*

1155 2.1.2. Negative finding; follow-up according to protocol

1157 *These boards also form the regional steering-groups for the study. They should preferably include
1158 surgeon, radiologist, and oncologist.

1161 **Appendix 3**

1162 **Guidelines for handling of detected recurrences in the COLOFOL study groups**

1166 If recurrence is suspected or verified, the patient-case should be evaluated in a regional
1167 multidisciplinary board* to offer the best available treatment for the patient (surgery, palliative
1168 chemo and/or radiotherapy, no treatment).

1169 In patients where a recurrence is diagnosed, a minimum requirement for treatment is
1170 recommended:

- Performance status of WHO 0 or 1 and ASA ≤3
- Sufficient liver and renal function
- Patient agrees to undergo surgery

1176 Contraindications for curative aiming surgery are:

- Disseminated carcinomatosis (e.g. Virchow's nodes or bone metastases)
- Multilobar lung metastases
- Performance status WHO >2 or ASA >4
- >6 liver segments involved or >75% tumour invasion of liver or all 3 hepatic veins involved
(approximity to the liver veins is not a contraindication in RFA treatment)
- Major liver insufficiency or Child's B or C liver cirrhosis with complications
- Patient declines surgery

1185 As a general recommendation patients should be included in ongoing controlled clinical treatment
1186 studies that would not interfere with COLOFOL.

1190 **1. Liver metastases**

1191 Patients with ≤4 liver metastases where a liver resection preserves >30% of liver parenchyma
1192 should be resected. Whether neoadjuvant/adjuvant chemotherapy should be given is up to the
1193 regional multidisciplinary board to decide. The treatment when >4 metastases are present or
1194 when <30% of functional liver parenchyma would be preserved after radical aiming surgery is a
1195 decision by the regional board. The use of local ablation methods
1196 (radiofrequency/cryotherapy/laser) to achieve radical destruction of known lesions is allowed,
1197 but not recommended for lesions that can be radically resected.

1200 **2. Lung metastases:**

1201 Patients with unifocal lung metastases without hilar nodes and not requiring pulmectomy
1202 should be resected or RFA treated in controlled clinical trials.

1205 **3. Local recurrences**

1206 If a radical (R0 or R1) resection is judged possible at the multidisciplinary board discussion – a
1207 resection is favoured. This includes extensive surgery like: peritoneal resection, abdominal
1208 wall resection, hysterectomy, cystectomy and pelvic exenteration if necessary and if patient is
1209 fit. En-bloc resections are mandatory. Surgery can be combined with chemoradiation,
1210 including IORT, if judged beneficial to the patient.

1213 **4. Multifocal recurrences**

1214 4.1. Synchronous liver and lung metastases:

1215 Patients fulfilling the criteria for treatment of liver or lung metastases above should also be
1216 evaluated for resections/ablation when both liver and lung metastases are present.
1217

1218 4.2. Lymph node metastases and synchronous liver and/or lung metastases:

1219 Radical aiming resections/ablations are not recommended as single treatment and should
1220 only be considered in combination with chemo/chemoradiation treatment performed in
1221 controlled clinical studies.

1222 4.3. Local recurrence and synchronous liver and/or lung metastases:

1223 Radical aiming resections/ablations are not recommended as single treatment and should
1224 only be considered in combination with chemo/chemoradiation treatment performed in
1225 controlled clinical studies.

1226 *These boards also form the regional steering-groups for the study. They should preferably
1227 include surgeons, radiologists, and oncologists.

1236 **Appendix 4**

1237

1238 **Quality of life instruments**

1239

1240 The effect of follow-up on health related quality of life will be assessed by three validated self-
1241 administered instruments, as used in other trials (Grunfeld et al. BMJ 1996;313:66-669)

1242

1243 • The British version of the SF-36 (Ware et al. Boston: Health Institute, New England Medical
1244 Center, 1993).

1245

1246 • The European Organisation for Research and Treatment of Cancer core quality of life
1247 questionnaire (EORTC QLQ-C30) (Aaronson et al. J Natl Cancer Instit 1993;85:365-376).

1248

1249 • And the hospital anxiety and depression scale (Zigmond and Snaith Acta Psychiatr Scand
1250 1983;67:361-370).

1251

1252

1253 **Appendix 5**

1254

1255 **Members of the COLOFOL study-group**

1256

1257 **Denmark**

1258 Søren Laurberg, Surg. Dept., Århus Univ. Hospital
1259 Henrik Toft Sørensen, Dept. Clin. Epid., Århus Univ. Hospital
1260 Mogens Rørbaek Madsen, Surgical Dept. A, Herning Centr. Hospital
1261 Henrik Harling, Surg. Dept. K, Bispebjerg Hospital
1262 Peer Wille-Jørgensen, Surg. Dept. K, Bispebjerg Hospital
1263 Peter Christian Rasmussen, Surg. Dept. Århus Univ. Hospital
1264 Dennis Tønner Nielsen, Dept. Radiology, Århus Univ. Hospital
1265 Mette Vinther Skriver, Århus
1266 Per Vadgaard Andersen, Dept Surgery, Svenborg
1267 Hans B Rahr, Dept Surgery A, Odense University Hospital
1268 Knud Erik Jensen, Dept Surgery, Esbjerg
1269 Erling Østergaard, Viborg Hospital
1270 Per Jess, Dept Surgery, Hillerød Hospital
1271 Per Gandrup, Dept Surgery A, Aalborg
1272 Henrik Christensen, Dept. of Surgery L, Århus Hospital
1273 Allan G. Pedersen, Dept. Of Surgery, Randers Hospital

1274

1275 **Sweden**

1276 Nils Lundqvist, Surgical Dept. Norrtälje Hospital
1277 Lars Pahlman, Surg. Dept. Uppsala Univ. Hospital
1278 Peter Naredi, Dept. of Surg., Umeå Univ. Hospital
1279 Birger Sandzen, Dept. of Surg., Umeå Univ. Hospital
1280 Gudrun Lindmark, Surg. Unit., Helsingborg Lasarett
1281 Ingvar Syk, Surg. Clinic, Univ. Hospital, Malmö
1282 Kennet Smedh, Dept. of Surgery, Central Hospital, Västerås
1283 Lennart Blomqvist, Dept. Radiology, Solna
1284 Michael Goldinger, St. Görans Hospital, Stockholm
1285 Anna Martling, Dept of Surgery, Karoliska Solna, Stockholm
1286 Johan Ottoson, Dept. of Surgery, Central Hospital Kristianstad
1287 Monika Svanfeldt, Gastrocentrum, Karolinska Huddinge, Stockholm
1288 Stefan Dedorson, Surgical Clinic, Södertälje Hospital
1289 Mats Bragmark, Dept. of Surgery, Danderyd Hospital
1290 Jonas Bengtson, Dept. of Surgery, Sahlgrenska University Hospital, Göteborg
1291 Helena Laurell, Dept. of Surgery, Mora Hospital
1292 Yngve Raab, Dept. Of Surgery, Södersjukhuset, Stockholm
1293 Christoffer Odensten, Dept. Of Surgery, Sunderby Hospital, Luleå

1294

1295

1296 **Poland**

1297 Jósef Kladny, Clinic of Gen. and Onco. Surgery, Pomeranian Medical University
1298 Adam Dziki, Dept. of Surgery, Medical University of Lodz

1299

1300 **Uruguay**

1301 Luis A. Carriquiry, Dept. of Surgery, Maciel Hospital, Montevideo

1302

1303 **UK**

1304 Andrew Renahan, Inst. of Canc. Stud., Manchester

1305

1306

1307 This group will be expanded according to the participation of centres.

1308

1309 **Appendix 6**

1310

1311 **Database forms**

1312

1313

PRE-RANDOMISATION DATASHEET

PERIOPERATIVE FORM

PatientID.: 1

Last name:

Initials:

Gender:



Male



Female

INCLUSION CRITERIA

Birthday:

(dd-mm-yy)

EXCLUSION CRITERIA

Clinical diagnosis of HNPCC or FAP:

-

Local excision for colorectal cancer:

-

Life expectancy less than 2 years:

-

Inability to comply with the control
or intense follow-up programme:

-

Participates in other clinical trials interfering
with the control programmes:

-

GENERAL HEALTH

Ever diagnosed with one of the following diseases:



Diabetes



AMI, hypertension or other heart diseases



Pulmonary disease



Multiple sclerosis



Cerebrovascular disease



Other major disease

- specify:

LIFE STYLE

Do patient smoke:

-

Do patient have a daily alcohol consumption:

-

PERIOPERATIVE DIAGNOSTICS

Lung metastases (X-ray, CT, MR):

-

Liver metastases (CT, MR):

Rectal cancer:

Distance from anal verge
to the lower tumour edge (<= 15 cm):

 cm.

Initially judged inoperable (fixed tumor):

Preoperative radiation:

Preoperative chemotherapy:

SURGERY

Date of operation:

 (dd-mm-yy)

Elective or emergency operation:

Tumour perforation:

Tumour fixation:

Localization of colorectal cancer at operation:

- Right side
- Transversum
- Left side
- Rectum (<=15 cm)

Temporary ostomy:

Permanent ostomy:

Biological bank:

Blood sample to biological bank:

Sample tissue to biological bank:

PATHOLOGY

Number of nodes examined (all patients):

Number of nodes with metastases:

Distance from tumour to the
circumferential margin of resection
(for rectal cancer the minimum distance):

 mm

Staging

- R0 (Macroscopic and microscopic local
radicality. No distant metastases.):

- Dukes' stage:

- TNM T-stage:

- TNM N-stage:

- TNM M-stage:

POSTOPERATIVE COURSE (<=30 days)

Preoperative CEA level:

Postoperative CEA level (4 weeks):

Severe postoperative complications:

- Stroke
- Myocardial infarction or heart deficiency
- Pulmonary embolus
- Healing complications + laboratory
- Healing complications without laboratory
- Anastomosis + reoperation
- Anastomosis without reoperation
- Other serious events

- specify:

Blood transfusion during the hospitalization:

Referred to postoperative radiotherapy:

Adjuvant chemotherapy planned:

Colonoscopy for clean colon or X-ray of Barium performed preoperatively or planned 3 months after surgery:

Signed consent for participation:

Date of filling in the form: (dd-mm-yy)

1314

1315

1316

1317

FOLLOW-UP

PatientID.: 1

Date of conclusion of this visit: (dd-mm-yy)

Follow-up:

-

- If not planned, which cause/symptom:

- Pulmonary symptoms
- Jaundice symptoms
- Gastrointestinal symptoms
- Pain
- Suspicious of local recurrence
- Other

- specify:

Examinations (planned or interval)

CEA:

-

- Reason if not performed:

- CEA level:

- level changed:

-

Multislice CT of liver / MR:

-

- Reason if not performed:

CT of lungs / X-ray:

-

- Reason if not performed:

Positive findings on any examinations
above leading to further examinations:

-

- MR abd., MR pelvis
- CT thorax
- PET
- Repeated CEA
- Rigid sigmoidoscopy
- Evaluation in multidisciplinary board

Outcome

Recurrence of colorectal cancer denied:

-

Recurrence of colorectal cancer suspected:

-

Recurrence of colorectal cancer operable:

-

Location of metastasis:	<input type="text"/> - <input type="button"/>
Recurrence of colorectal cancer confirmed:	<input type="text"/> - <input type="button"/>
- How many:	<input type="text"/>
- Size of the largest (maximum):	<input type="text"/> mm
Metachronous cancer determined:	<input type="text"/> - <input type="button"/>
Blood samples	
Blood samples to biological bank:	<input type="text"/> - <input type="button"/>
Tissue samples to bio bank:	<input type="text"/> - <input type="button"/>

1318
1319

1320

ENDPOINT / Termination

PatientID:

Endpoint

Reason for leaving:

- Death:

- Death related to examinations or complications:

Examinations within the protocol

- specify:

Complications to secondary surgery

Complications to radiation

Complications to chemotherapy

Recurrence of colorectal cancer:

Date of leaving study: (dd-mm-yy)

1321

1322

1323

1324 **Appendix 7**

1325

1326 **Steering-group members:**

1327

1328 Peer Wille-Jørgensen, Bispebjerg Denmark

1329 Søren Laurberg, Århus, Denmark

1330 Dennis Tønner Nielsen, Århus, Denmark

1331 Ingvar Syk, Malmö, Sweden

1332 Kennet Smedh, Västmanland, Sweden

1333 Adam Dziki, Lodz, Poland

1334 Andrew Renahan, UK

1335

1336

1337 **Appendix 8**

1338

1339 **Monitoring committees**

1340

1341 **Study monitoring:**

1342 To be appointed by Danish Colorectal Cancer Group

1343 To be appointed by Swedish Colorectal Society

1344 To be appointed from UK and the Netherlands

1345

1346

1347 **Quality of diagnostic methods committee:**

1348

1349 Dennis Tønner Nielsen

1350 Overlæge

1351 Radiologisk afd. R

1352 Århus Universitetshospital

1353 Århus Sygehus

1354 Nørrebrogade 44

1355 8000 Århus , Århus

1356 Denmark

1357

1358

1359 Lennart Blomqvist M.D. Ph.D.

1360 ADR Centrale röntgen

1361 Karolinska Universitetssjukhuset, Solna

1362 171 76 Stockholm,

1363 Sweden

1364

1365 **Appendix 9**

1366

1367 **Patient Information and Layperson protocol**

1368

1369 **(For Denmark)**

1370

1371 **Det videnskabelige projekt COLOFOL: "Hyppig kontrol efter operation for kræft i tyk- eller endetarm ?"**

1372

1373

1374 Vi ved, at nogle patienter får tilbagefald af sygdommen, selvom alt kræftvæv tilsyneladen-de blev fjernet ved

1375 operationen. Det er derimod usikkert, om man ved hospitalskontrol kan opdage tilbagefaldet før patienten

1376 får nye symptomer, og på den måde forbedre helbredel-sesmulighederne. Derfor er der i øjeblikket ikke

1377 retningslinier for, om og hvordan en even-tuel kontrol efter operation bør tilrettelægges. De kirurgiske

1378 afdelinger har således meget forskellige kontrolprogrammer, og nogle slet ingen.

1379

1380 I de senere år er der kommet bedre skanningsmetoder til (især CT-skanning), og det er muligt, at disse

1381 metoder kan forbedre et kontrolprogram. Vi ved det ikke, og vi ved heller ikke hvor hyppigt vi skal kontrollere

1382 efter operation. Vi kan kun få et svar på det spørgsmål gennem et lodtrækningsforsøg: hyppig kontrol eller

1383 kontrol med lange mellemrum. Der er fordele og ulemper ved begge:

1384

1385 Fordelen ved hyppig kontrol er, at et tilbagefald muligvis kan opdages i tide, så helbredel-se er mulig .

1386 Ulemperne er, at nogle patienter bliver ængstelige ved udsigten til hyppige sygehusbesøg; af og til finder

1387 man noget ved undersøgelserne, der alligevel ikke viser sig at være kræft, og undersøgelsesmetoderne vil

1388 næppe kunne afsløre tilbagefaldet, hvis det er meget lille. Fordelen ved sjælden kontrol er, at man slipper for

1389 at blive mindet om den kræftsygdom, man er blevet opereret for. Ulempen er, at helbredelsesmulighederne

1390 muligvis ikke er gode, hvis man først behandles, når der er kommet symptomer på tilbagefald.

1391

1392 Vi spørger derfor, om du vil være med i vort forsøg. Du er velkommen til at tage dine pårørende med til

1393 samtalen, og vedlagt dette brev finder du píecen: "Før du beslutter dig". Vi vil understrege, at din beslutning

1394 ikke får betydning for din behandling og kontrol. Hvis du siger ja, er det din fulde ret at trække dig ud igen på

1395 et hvilket som helst tidspunkt siden hen, uden det får indflydelse på din behandling. Hvis du siger nej, vil du

1396 blive tilbuddt kontrol efter din afdelings normale procedure. Vi kan desværre ikke tilbyde dig hyppig kontrol

1397 uden for projektet – dette program er dyrt, vi ved ikke om det virker og må derfor prioritere vores ressourcer.

1398

1399 Der vil blive trukket lod om hyppig kontrol: 6,12, 18, 24 og 36 måneder efter operationen i form af CT-

1400 skanning eller røntgenundersøgelse af lungerne + CT-skanning af leveren + en blodprøve. I den anden

1401 gruppe med sjælden kontrol vil de samme undersøgelser blive foretaget 12 og 36 måneder efter

1402 operationen.

1403

1404 Ved hyppig CT-skanning vil du blive utsat for en forøget, men dog stadig ganske lille stråledosis (ca. 10

1405 millisievert, hvilket svarer til to gange den bestråling, vi normalt utsættes for fra omgivelserne på et år).

1406 Risikoen for, at denne stråledosis fører til kræftudvikling er meget lille – mellem 1:3000 og 1:16.000.

1407 Risikoen for, at en dansker får kræft i løbet af sin levetid er til sammenligning 1:4.

1408

1409 Projektet kaldes COLOFOL; det er økonomisk støttet af Nordisk Cancer Union, ingen enkeltpersoner har

1410 økonomiske interesser i projektet, som foregår i flere europæiske lande.

1411

1412 Med venlig hilsen

1413

1414 xxxxxxxx

1415 overlæge

1416 xxx - sygehus

1417

1418

1419

1420

1421

1422

1423

Peer Wille-Jørgensen
Overlæge dr.med.
Projektleder
Bispebjerg Hospital

1424 Navn CPR (label)
1425
1426
1427
1428
1429
1430
1431
1432 Jeg bekræfter hermed at have modtaget skriftlig og mundtlig information om deltagelse i
1433 undersøgelse af værdien af efterkontrol efter behandling for tarmkræft.

1434
1435 Med min underskrift godkender jeg deltagelse i COLOFOL projektet.
1436

1437
1438
1439
1440
1441 xxxxxx den / 200
1442

1443
1444
1445
1446

underskrift
1447

1448
1449
1450
1451 Modtaget af læge:
1452
1453

1454
1455

1456 Ikke-videnskabelig beskrivelse af COLOFOL projektet.
1457
1458
1459
1460 Værdien af kontrol efter operation for kræft i tyk-og endetarm er uafklaret, men de nyeste analyser af de
1461 videnskabelige resultater tyder på, at man ved mere intensiv kontrol kan opnå en forlænget overlevelse. Det
1462 ser desuden ud til, at det man skal lede efter er sygdomstilbagefald i leveren (levermetastaser), der er
1463 tilgængelig for behandling i en del tilfælde.
1464
1465 I øjeblikket er der ingen faste retningslinier for kontrol i Danmark og alle variationer af kontrolmetoder og
1466 intervaller anvendes på de forskellige sygehuse. Kontroller er dyre og kan medføre unødig ængstelse for
1467 patienterne, hvorfor en afklaring af de optimale kontrolintervaller og metoder er vigtig for både patienter og
1468 samfund.
1469
1470 Der er derfor planlagt et internationalt multicenterstudie hvor man ønsker afklaret hvorvidt et
1471 kontrolprogram, der indebærer scanning og/eller røntgenundersøgelse af lever og lunger, samt en
1472 blodprøve, der kan give mistanke om tilbagefald har nogen værdi.
1473
1474 Patienterne vil efter informeret samtykke ved lodtrækning blive placeret i to grupper. èn hvor
1475 kontrolprogrammet foretages efter 12 og 36 måneder og en anden, hvor programmet foretages efter 6, 12,
1476 18, 24 og 36 måneder.
1477
1478 Såfremt der konstateres tilbagefald vil den videre behandling blive fastlagt af et tværfagligt panel bestående
1479 af kirurger, medicinske kræftlæger, og røntgenlæger.
1480
1481 Undersøgelsen opstartes som et multicenter studie i Sverige, Danmark, England og Holland.
1482 De forberedende arbejder til undersøgelsen er støttet af Nordisk Cancerunion med 175.000 kr
1483
1484 Dansk version af COLOFOL protokol vedlægges.
1485
1486 København den 12/10 2004
1487
1488
1489 Med venlig hilsen
1490
1491
1492
1493
1494 Peer Wille-Jørgensen
1495 Projektleder
1496 Overlæge, dr.med.
1497 Kirurgisk afdeling K
1498 H:S Bispebjerg Hospital

1502
1503

Patientinformation

1504 Du tillfrågas härmed om Du vill delta i en forskningsstudie. Du har fått information om att vi har opererat bort en
1505 cancer tumör i Din tjocktarm. Tumören har blivit radikalt bortopererad. Trots detta finns en risk att Din tumör kan
1506 ha spridit sig till olika organ. Inför operationen undersökte vi Dina lungor och lever och under operation har vi
1507 undersökt dessa organ också och kunnat konstatera att det inte finns någon spridning. Det kan dock finnas en
1508 mikroskopisk spridning, vilket innebär att det finns tumörceller som vi inte kan upptäcka idag. Skulle så vara
1509 fallet finns möjlighet att upptäcka dem genom ett kontrollerat uppföljningsprogram.

1510 I Sverige kontrolleras patienterna regelbundet på mottagningen med ungefär 1 års mellanrum. Frågan har
1511 uppstått om man behöver kontrollera våra patienter ännu oftare och därför görs en stor studie i Sverige, där vi
1512 jämför uppföljning två gånger postoperativt (1 år och 3 år) med att följa våra patienter var 6:e månad. Denna
1513 studie görs tillsammans med kirurger inom de nordiska länderna, Holland och England. Vid varje
1514 uppföljningstillfälle kommer vi att ta blodprover, där vi specifikt tittar på leverfunktionen. Vi kommer att ta
1515 speciella tumörmarkörer samt ta till vara blodprov som skall sparas för att vi vid ett senare tillfälle skall kunna
1516 titta om specifika idag icke kända tumörmarkörer har blivit stegrade. Vid varje besökstillfälle kommer vi att ta 20
1517 ml blod för dessa analyser. Hälften av dessa blodprover kommer att sparas i en s k biobank, vilket innebär att vi
1518 skall kunna gå tillbaka och titta på de specifika tumörmarkörerna. Vi kommer också att undersöka Din lever med
1519 datortomografi eller ultraljud samt undersöka Dina lungor. En undersökning med datortomografi motsvarar en
1520 stråldos på i storleksordningen 2,3 års bakgrundsbestrålning. Att undersöka just lever och lungor beror på att det i
1521 första hand är dit som en tumör brukar sprida sig.
1522

1523
1524 I samband med den här undersökningen kommer vi att be Dig fylla i en enkät om hur Du upplever att bli
1525 undersökt på detta sätt för att om möjligt kunna hitta en tumörspridning som vi kan bota.
1526

1527 Personuppgiftsansvarig är Uppsala universitet. Enligt personuppgiftslagen (PUL) har Du rätt att gratis en gång per år få
1528 ta del av de uppgifter om Dig som hanteras och vid behov få eventuella fel rättade. Om Du vill ha detta utdrag,
1529 kontakta undertecknad, Lars Pahlman.
1530

1531 Det står Dig helt fritt att tacka nej. Du kan också när som helst tacka nej under den pågående studien utan att
1532 ange varför. Skulle Du avstå från att delta eller icke vilja fortsätta i studien, kommer detta inte att menligt
1533 påverka Dina möjligheter till ett gott omhändertagande.
1534

1535
1536
1537
1538 Lars Pahlman
1539 *Professor*
1540 Kirurgiska kliniken, Akademiska sjukhuset, 751 85 Uppsala
1541 E-post: lars.pahlman@surgsci.uu.se
1542 Tel: 018-611 46 75
1543

1557 **Patientinformation (for Poland)**

1558

1559

1560 Szanowna/y Pani/Panie

1561

1562 Chcielibyśmy Pani/Panu zaproponować uczestnictwo w projekcie badawczym „**Pragmatyczne
badanie nad oceną częstości badań diagnostycznych po resekcji jelita u pacjentów z II i III
stopniem zaawansowania gruczolakoraka jelita grubego - badanie randomizowane,
wieloośrodkowe.**” zwanym dalej COLOFOL.

1566

1567 Projekt ten jest związany z Pani/Pana chorobą. Tak dla każdego człowieka przykra diagnoza jaką
1568 niedawno Pani/Pan usłyszeli wiąże się z wieloma działaniami jakie personel medyczny podejmuje
1569 wyłącznie w jednym, najważniejszym celu. Tym celem jest całkowite wyleczenie Pani/Pana z
1570 choroby nowotworowej jelita grubego. Najważniejszym elementem tego celu jest leczenie
1571 operacyjne, któremu już zostałał Pani/Pan poddana/y. Jeśli istnieje taka konieczność zgodnie z
1572 obowiązującymi standardami przy pewnym stopniu zaawansowania choroby nowotworowej należy
1573 też poddać pacjenta terapii dodatkowej przedoperacyjnej, bądź pooperacyjnej. Z kolej przychodzi
1574 czas na etap kolejny nie mniej ważny. Etapem tym jest okres obserwacji pacjenta po udanym
1575 leczeniu radykalnym. W tym czasie obserwuje się pacjenta i wykonuje pewne badania, aby
1576 sprawdzić czy nie nastąpił nawrót choroby. Jest to bardzo ważny okres, gdyż w razie wykrycia
1577 nawrotu choroby medycyna ma możliwości aby z tym walczyć i pozbyć się choroby.

1578 Do tej pory nie ma obowiązujących wytycznych ani standardów jakie badania i jak często
1579 przeprowadzać aby wykrywanie nawrotu choroby było jak najszybsze, jak najefektywniejsze a
1580 jednocześnie nie utrudniało życia pacjenta. Istnieje wśród lekarzy duża zgodność co do tego jakie
1581 badania należy wykonywać. Są to:

- 1582 • tomografia komputerowa jamy brzusznej, jest nowoczesnym badaniem z wykorzystaniem
1583 promieniowania rentgenowskiego
- 1584 • badanie poziomu marker'a nowotworowego o nazwie antygen karcynombrionalny (CEA),
1585 jest związane z pobraniem niewielkiej ilości krwi
- 1586 • zdjęcie rentgenowskie klatki piersiowej
- 1587 • badanie ultrasonograficzne jamy brzusznej

1588 Niestety nikt do tej pory nie określił jak często badania te powinno się wykonywać. Badanie, w
1589 którym proponujemy udział ma na celu określenie czy częstsze wykonywanie badań ma wpływ na
1590 długofalowe wyniki leczenia i jakość życia pacjenta.

1591 Po wyrażeniu zgody na uczestnictwo w badaniu będzie Pani/Pan przydzielona/y do jednej z dwóch
1592 grup Obie gruby pacjentów będą objęte obserwacją pooperacyjną, w obu grupach będziemy
1593 wykonywać te same badania diagnostyczne a mianowicie tomografię komputerową jamy brzusznej,
1594 zdjęcie rentgenowskie klatki piersiowej, oznaczanie poziomu markera nowotworowego oraz

1595 badanie ultrasonograficzne jamy brzusznej. Różnica będzie polegała na częstotliwości wykonywania
1596 badań. a mianowicie

1597 **1. schemat o mniejszej częstotliwości badań**

- 1598 • CEA okołoperacyjnie i jeden miesiąc po operacji
1599 • CEA, CT i rtg klatki piersiowej 12 i 36 miesięcy po leczeniu operacyjnym

1600 **2. schemat o większej częstotliwości badań:**

- 1601 • CEA okołoperacyjnie i jeden miesiąc po operacji
1602 • CEA, CT i rtg klatki piersiowej 6, 12, 18 i 36 miesięcy po leczeniu operacyjnym.

1603

1604 Jak Pani/Pan widzi niezależnie od przydziału do gruby badawczej będą Państwo objęci
1605 skrupulatną i wnikliwą opieką pooperacyjną, której celem jest Pani/Pana pełne wyleczenie.
1606 Zapewniamy Pani/Panu anonimowość i pełną ochronę danych osobowych w razie
1607 przystąpienia do badania.

1608 Zapewniamy, iż w każdej chwili bez podania powodu mogą Państwo zrezygnować z
1609 uczestnictwa w badaniu co nie będzie oznaczało, iż nie będziemy się państwem nadal
1610 opiekować z tą sama troską o Państwa zdrowie.

1611 Zapewniamy, iż mimo nie wyrażenia zgody na uczestnictwo w badaniu będą Państwo objęci
1612 opieką naszej Kliniki.

1613

1614 Jednocześnie chcielibyśmy, aby Państwo pamiętały, iż wyrażenie zgody na uczestnictwo w
1615 badaniu będzie się wiązało z:

- 1616 • koniecznością wizyt w Klinice (o różnej częstotliwości w zależności od przynależności do
1617 różnej grupy badawczej),
1618 • wykonaniu badań diagnostycznych (w tym z użyciem promieni rentgenowskich),
1619 • możliwości kontaktowania się z państwem telefonicznie.

1620 Postaramy się aby ewentualne uczestnictwo było dla Państwa jak najmniej kłopotliwe.

1621

1622 Z poważaniem

1623

1624 **Patient information in Spanish**

1625

1626 INFORMACION AL PACIENTE

1627

1628 **Estudio científico “ COLOFOL”: el mejor intervalo entre los examenes de control luego de una operacion por cancer colorrectal – un estudio colaborativo entre cirujanos daneses, suecos, británicos, holandeses, polacos y uruguayos-**

1631

1632 Aunque la operación que le ha sido realizada ha sido exitosa y ha eliminado todos los tejidos afectados por el tumor, de acuerdo al criterio del cirujano, siempre existe un cierto riesgo de que la enfermedad reaparezca en el futuro. Existen en el mundo distintos programas de control que buscan despistar tempranamente la reaparición de la enfermedad para poder tratarla adecuadamente y a tiempo.

1633 Pero no sabemos aun con que frecuencia y qué estudios son los más efectivos para lograr ese objetivo. No

1634 tendría sentido realizar estudios cada poco tiempo dado los gastos y las molestias que ello podría originar al

1635 paciente.

1636 Por ello un grupo de investigadores europeos ha diseñado el presente estudio que busca establecer cual es

1637 el mejor de dos esquemas de seguimiento con respecto al mejor futuro para el paciente y con el menor

1641 gasto para la sociedad.

1642 Un grupo de médicos uruguayos hemos solicitado participar en este estudio y nuestro pedido ha sido

1643 aceptado, por lo que incluiremos nuestros pacientes al mismo tiempo que los suecos, daneses, holandeses,

1644 polacos e ingleses.

1645 Por eso le pedimos que acepte participar en este estudio. Decida participar o no , Ud. será tratado y

1646 controlado de acuerdo a los criterios de su cirujano y su oncólogo. Pero si decide hacerlo, Ud. será

1647 asignado luego de la intervención quirúrgica a uno de los dos programas de seguimiento y deberá cumplir

1648 con los estudios, que le solicite su cirujano, en los plazos fijados.

1649 Los estudios a realizar en cualquiera de los dos programas son similares: estudios de sangre y tomografías

1650 o resonancias magnéticas, variando solamente los plazos en los que se realizarán. Estos estudios son los

1651 que habitualmente se realizan en nuestro país para todos los pacientes operados de cáncer colorrectal

1652 como Ud. Aceptando participar en el estudio, Ud. se compromete sólo a realizarse esos estudios en los

1653 plazos que le correspondan de acuerdo al programa que le sea asignado, sea cada a los 6, 12, 18, 24 y 36

1654 meses durante 3 años, o solo a los 12 y 36 meses en el mismo plazo. En cualquiera de los dos casos, la

1655 dosis de radiación que implica la realización de tomografías computadas es mínima y no ofrece riesgos para

1656 su futuro. Si Ud. no acepta participar o desiste de hacerlo en cualquier momento luego de haber aceptado,

1657 se le seguirán realizando estudios similares a criterio de su cirujano u oncólogo, sin que se resienta por ello

1658 la calidad de su atención médica.

1659 Este estudio no persigue otro fin que determinar con precisión científica cual es el mejor esquema de

1660 seguimiento para los pacientes operados con éxito por cáncer colorrectal, como es su caso. Deseamos

1661 dejarle claro finalmente:

1662 - que este estudio sólo persigue un interés científico y que ninguna persona o institución tiene ningún

1663 tipo de interés económico en su realización.

1664 - que su participación no lo hace acreedor a ningún tipo de retribución personal , salvo

1665 eventualmente un viático de transporte para aquellos pacientes que vivan en el Interior del país.

1666 - que sus datos personales serán resguardados bajo secreto profesional y adecuadamente

1667 codificados en una base de datos central en Dinamarca

1668

1669 Esperamos su consentimiento. Ante cualquier duda no vacile en comunicarse con el Dr. Luis A. Carriquiry,

1670 investigador principal del proyecto en Uruguay (tel 099 610926)

1671

1672 Otorgo mi consentimiento

1673

1674 Firma..... Nombre.....

1675

1676 No otorgo mi consentimiento

1677

1678 Firma..... Nombre

1679

1680

1681

1682

1683

1684

1685 **Patientinformation and layperson protocol in English (translated from the Danish Version)**

1686

1687

1688 **The scientific investigation COLOFOL: The Interval beween control-examinations after operation for**
1689 **colorectal cancer.**

1690

1691 We know some patients will experience recurrent disease, despite all malignant tissue apparently were
1692 remoed at the operation. It is although uncertain whether you by means of hospital control investigations can
1693 diagnose these recurrencies before symptoms occur thus improving the chance of cure. The guidelines for
1694 which kind of control programmes to apply after the operation are thus variable from hospital to hospital.

1695

1696 During the later years better scanning methods have become available, and it is possible, that these
1697 methods can improve the control programmes. We do not know and we also do not know how often the
1698 controls are to be performed. We can only get an answer on this though a randomised study where the
1699 interval between controls are descided by the draw of a lot.

1700

1701 The advantage by a frequent control is that a recurrence eventually can be discovered in such a due time
1702 that cure is possible. The disadvantage is that some patients dislike frequent visits to hospitals, and
1703 sometime you find something which finally shoes up to be non recurrent disease. The control investigations
1704 might not find the recurrence if it is very small. The advantage by a less frequent control is that you are not
1705 reminded of the malignant disease, you have been operated for. The disadvantage is that the possibilities for
1706 cure might be less if treatment is postponed until symptoms occur.

1707

1708 We therefore ask whether you will participate in our trial. You are welcome to bring consult relatives and as
1709 an addition to this letter, you find the brochure "Before I Decide". We want to emphasize, that your decision
1710 will have no influence on your treatment and control. If you accept, it is your right to withdraw your consent at
1711 any time without this will have any influence on your treatment. If you say no, you will be offered control
1712 according to the normal procedures in the department. We are not able to offer you frequent control outside
1713 the trial. This programme is expensive, and we do not know whether it works, thus we have give priority
1714 according to our resources

1715

1716 A lot wil be drawn in frequent control: 6, 12, 18, 14, 36 months after the operation a CT-scan or X-ray of the
1717 lungs, a CT-scan of the abdomen, and a blood sample will be performed. In the group of infrequent control
1718 the same investigations will be performed at 12 and 36 months after the operation

1719

1720 By frequent CT-scan you will be exposed to an elevated, but still very small dose of radiation (about 10
1721 millisievert, which is double the dose, you normally gets from the environment per year). The risk this dose
1722 should lead to cancer is betwen 1:3000 to 1:16,000. The risk an average person develops cancer during
1723 his/her lifetime is about 1:4.

1724

1725 The trial is called COLOFOL and has been supported by the Nordic Cancer Union. No individual persons or
1726 companies have any economic interests in the trial, which is conducted in several European Countries.

1727

1728 Sincerely

1729

1730 xxxxxxxxxxxx

1731 Consultant surgeon

xxxxxxxxxxxxxxxxxx

Country co-ordinator, COLOFOL

1732

1733 **Non-scientific description of the COLOFOL trial (layman protocol)**

1734

1735

1736 The value of control after operation for colorectal cancer is mostly unknown, but the newest

1737 analyses of the scientific results indicate that a more intensive control leads to a better survival.

1738 Besides this there are indications of that the thing to look for is recurrence in the liver (liver

1739 metastases) which is sometimes cureable.

1740

1741 The guidelines for control in Europe vary from hospital to hospital. Controls are expensive and can

1742 lead to unnecessary anxiety for the patient. It is thus important to clarify the optimal control

1743 intervals and methods for both patients and society

1744

1745 Therefore an international multicenter trial has been planned in which we want to clarify whether a

1746 control programme including scanning and/or X-ray of lungs and liver + a blood test, which can

1747 indicate recurrence are of any value.

1748

1749 After informed consent has been obtained the patients will after drawing a lot be placed in one of

1750 two groups. One where the programme will be run after 12 and 36 months or another where the

1751 programme will be run at 6, 12, 18, 24, and 36 months after surgery.

1752

1753 If recurrence is discovered the further treatment will be decided by a multidisciplinary team

1754 consisting of surgeons, oncologists, and radiologists.

1755

1756 The trial will be performed in Denmark, Sweden, Poland and eventually UK and Holland. The planning

1757 of the study has been supported by the Nordic Cancer Union by 25,000 EUROS

1758

1759 **Appendix 10**

1760

1761 **Internet randomisation**

1762

1763 The randomisation will take place over the Internet via a server placed at Aarhus University
1764 Hospital, Denmark. The server contains a randomisation programme, which each centre will gain
1765 access to via a username and password. When logging on to the randomisation site, each centre
1766 must key patient data on all patients, who have given their consent and who fulfil the inclusion
1767 criteria for the study. After keying the data, a randomisation code will be provided.
1768 The data is encrypted before the information is transmitted over the Internet.

1769

1770 **The project's database**

1771

1772 A database for the project will be established, and this will also be placed at Aarhus University
1773 Hospital, Denmark. The Danish Board of Registry has approved the database. Access to the
1774 database can be gained through the project's homepage, by providing a valid username and
1775 password. Keying of baseline- and follow-up data will be carried out over the Internet using a
1776 standard web-browser, so no programmes need to be installed on the computers located at the
1777 centre. A number of validation procedures will be installed in order to ensure a high data quality.
1778 There will be sent out reminders of all follow-up visits and examinations, and data from these will
1779 also be keyed via the Internet. Each centre will be able to log on to the database via the homepage
1780 at any time in order to see descriptive data and number of included patients for own centre as well
1781 as for the entire study population. The database will ensure that data is available for statistical
1782 analysis immediately after termination of the study.

1783

1784

1785

1786

1787 **Appendix 11**

1788

1789 **Approval from Ethical Committees**

1790

KOMISJA BIOETYKI UNIWERSYTETU MEDYCZNEGO W ŁODZI
Al. Kościuszki 4, 90-419 Łódź, tel. / fax. 6321485
Wydział Wojskowo – Lekarski, ul. Żeligowskiego 7/9, 90-752 Łódź, tel./fax. 6324087

**UCHWAŁA KOMISJI BIOETYKI
O PROJEKCIE EKSPERYMENTU MEDYCZNEGO
numer RNN/185/05/KB z dnia 10.05.2005 r.**
(przy korespondencji dotyczącej niniejszej decyzji prosimy powoływać się każdorazowo na powyższy numer i datę Uchwały)

Wnioskodawca badania:

Prof.dr hab.med. Adam Dziki, kierownik Kliniki Chirurgii Ogólnej i Kolorektalnej Uniwersytetu Medycznego w Łodzi

Tytuł badania:

„Pragmatyczne badanie nad oceną częstości badań diagnostycznych po resekcji jelita u pacjentów z II i III stopniem zaawansowania gruczolakorka jelita grubego – badania randomizowane wielośrodkowe”

Na podstawie art. 29 ustawy z dnia 5 grudnia 1996 r. o zawodzie lekarza (Dz.U. z 1997 r. Nr 28 poz.152 wraz z późniejszymi zmianami), zarządzenia Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. w sprawie szczegółowych zasad powoływania i finansowania oraz trybu działania komisji bioetycznych (Dz.U.Nr 47 poz. 480), ustawy o prawie farmaceutycznym z dnia 20 kwietnia 2004 r. (Dz.U.Nr 92 poz. 882) oraz Zarządzenia Nr 13 Rektora Uniwersytetu Medycznego w Łodzi z 18 października 2002 r. wraz z Aneksem nr 1 z dnia 31 maja 2004 r., Komisja Bioetyki Uniwersytetu Medycznego w Łodzi (wypełniając zobowiązania ICH GCP) na posiedzeniu w dniu 10.05.2005 r. przeanalizowała wniosek, wysłuchała opinii recenzenta o przedstawionym projekcie badania i w wyniku przeprowadzonej dyskusji oraz tajnego głosowania

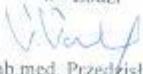
podjęła uchwałę o
pozytywnym zaopiniowaniu tego wniosku

bez zastrzeżeń

Do Komisji wpłynęły następujące dokumenty:

- Wniosek badacza
- Plan pracy
- Informacja dla pacjenta
- Formularz świadomej zgody pacjenta

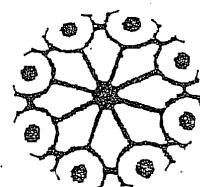
Przewodniczący
Komisji Bioetyki Uniwersytetu Medycznego
w Łodzi


Prof.dr hab.med. Przedzisław Polakowski

1791

1792

**DE VIDENSKABSETISKE KOMITÉER FOR
KØBENHAVNS OG FREDERIKSBERG KOMMUNER**



Dato 27. december 2004
J.nr. (KF) 01-194/04

Komité 1 Komité 2

Overlæge dr. med. Peer Anders Wille-Jørgensen
H:S Bispebjerg Hospital
Kirurgisk afd. K
Bispebjerg Bakke 23
2400 København NV

Vedrørende projektet (KF) 01-194/04: "Kontrol efter operation for kolorektal cancer. Et randomiseret forsøg af to kontrolregimer".

De Videnskabsetiske Komitéer for Københavns og Frederiksberg Kommuner har d. d. bedømt ovennævnte projekt som værende i overensstemmelse med Lov om de videnskabsetiske komitéer.

Det henstilles, at De selv underretter de øvrige medlemmer af projektgruppen om bedømmelsen.

Komitéen skal anbefale, at komitéens journalnummer så vidt muligt påføres de skriftlige forsøgs-personinformationer m.v. og anføres i forbindelse med publicering af projektet.

Med venlig hilsen

Rikard Vrogaard

/Lisbeth Lundgren

Fælles sekretariat: Københavns Kommune, Sundhedsforvaltningen, Sjællandsgade 40,
2200 København N
Telefon: 35 30 34 02, 35 30 34 05, 35 30 34 07, 35 30 34 09
Telefax: 35 30 39 90

Dnr 2004-453



EPN

BESLUT
2005-02-01

Dnr 2004: M-453

BESLUT

Nämnden bifaller ansökningen med inkommen komplettering 2005-01-31 och godkänner med stöd av 6 § lagen (2003:460) om etikprövning av forskning som avser mänsklig forskning som anges i ansökan.

SÖKANDE FORSKNINGSHUVUDMAN

Uppsala Universitet
Box 256
751 05 Uppsala

Forskar som genomför projektet:

Lars Pahlman
Kirurgiska kliniken
Akademiska sjukhuset
751 85 Uppsala

UPPGIFTER OM FORSKNINGSPROJEKTET ENLIGT ANSÖKAN
INKOMMEN TILL NÄMNDEN 2004-11-23 SAMT INKOMMEN
KOMPLETTERING 2005-01-31.**Projektbeskrivning**

Uppföljning av colorectal cancer - en randomisering studie.

Regionala etikprövningsnämnden i Uppsala meddelar följande

Villkor:

Texten om personuppgiftslagen skall kompletteras med uppgift om kontaktperson.
Forskningsprojekten innebär att blodprover sparas i biobank. Nämnden erinrar om skyldigheten att inhämta s.k. informerat samtycke från provgivarna enligt 3 kap.1§ lagen om biobanker inom hälso- och sjukvården m.m. samt även vad som i övrigt följer av reglerna i nämnda lag.

Erinran

Godkännandet upphör att gälla om forskningen inte har påbörjats inom två år efter sluttidigt beslut.

BESLUTET FÅR ÖVERKLAGAS

Se bifogad anvisning.

På nämndens vägnar

Jerry Eriksson
Ordförande

Brita Karlström
Vetenskaplig sekreterare

Exp. till:

Forskar: Lars Pahlman
Forskningshuvudmannens behörige företrädare: stf.prefekt Olle Nilsson,
Institutet för kirurgiska vetenskaper, Akademiska sjukhuset, 751 85 Uppsala

1794
1795
1796

Adress	Telefon	Fax	E-post
Box 569 751 22 Uppsala	018-4717400	018-4717410	registrator@uppsala.cpn.se

EL CONSEJO DE LA FACULTAD DE MEDICINA DE LA UNIVERSIDAD DE LA REPÚBLICA EN SESIÓN ORDINARIA DE FECHA 22 DE NOVIEMBRE DE 2006, ADÓPTO LA SIGUIENTE RESOLUCIÓN:

49.

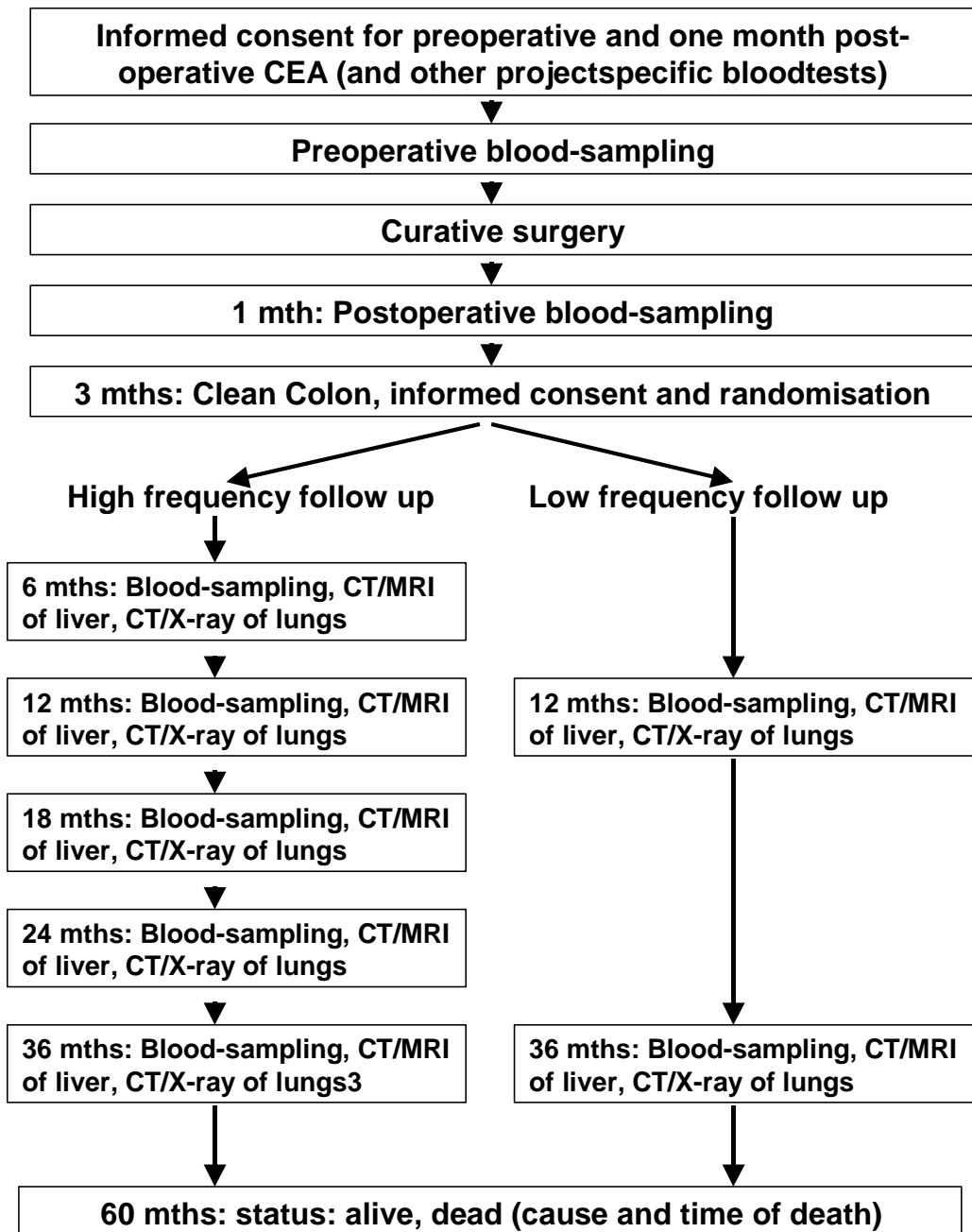
(Exp. N° 071140-001530-06) · Tomar conocimiento de que el Comité de Ética que estudia los Proyectos de Investigación aprobó el Proyecto titulado: "COLOFOL - un estudio pragmático para determinar la frecuencia de las pruebas diagnósticas de seguimiento en pacientes con cáncer colorrectal estadios II y III sometidos a resección curativa" cuyo investigador responsable es el Prof.Dr. Luis Carrizosa.- (9 en 9)

Comuníquese al investigador y pase a la Comisión de Ética para Proyectos (Depto. de Secretaría).


ARISELL TARDINO
ADM. I

1797

COLOFOL - Flowchart



COLOFOL – Inclusion and exclusion

Inclusion criteria:

- Radical surgery (R0-resection) for colorectal adenocarcinoma – with or without adjuvant treatment, and
- Age \leq 75 years, and
- Written informed consent, and
- “Clean colon” verified by perioperative barium enema or colonoscopy last 3 months post-surgery, and
- Tumour stage: II-III ($T_{\text{any}} N_{1-2} M_0$, $T_{3-4} N_{\text{any}} M_0$, Dukes' B - C)

Exclusion criteria:

- A clinical diagnosis of HNPCC (non hereditary polyposis colorectal cancer) or FAP (familial polyposis coli),
- Local resection for colorectal cancer (e.g., TEM-procedure),
- Life-expectancy less than 2 years due to concurrent disease (e.g., cardiac disease, liver cirrhosis),
- Inability to provide informed consent or refusal to do so,
- Inability to comply with the follow-up programme,
- Participation in other clinical trials interfering with the control-programmes – e.g. TRIALS on adjuvant therapy with CT endpoints
- Other or previous cancer (except for non-melanoma skin cancer)

Pre – or postoperative adjuvant chemotherapy and/or radiation therapy is allowed, as long as it is applied with same indications in the two groups.

Endoscopy is permitted, as long as equal in the two groups.

1805
1806

2. eStatistical Analysis Plan

1807

1808

1809

1810

1811 AIM

1812 To conduct a prospective multicenter randomised study comparing total mortality, cancer-specific
1813 mortality, recurrence-free survival, economic cost effectiveness, and quality of life (QOL) in
1814 patients receiving high-volume follow-up after radical resection for colorectal cancer, compared to
1815 patients receiving low-volume follow-up.

1816

1817 STUDY PROCEDURES

1818 *Recruitment and Eligibility*

1819 At each participating center, consecutive patients receiving radical surgery for colorectal cancer will
1820 be considered for inclusion. Those who are ineligible or who refuse consent will be followed
1821 observationally.

1822 *Inclusion criteria*

- 1823 • Radical surgery (resection) for colorectal adenocarcinoma – with or without adjuvant
1824 treatment
- 1825 • Age less than 75 years
- 1826 • Provision of written informed consent for participation.
- 1827 • “Clean colon” verified by perioperative barium enema or colonoscopy performed 3 months
1828 post surgery, at the latest
- 1829 • Tumor stage: T2-T4, Nany, M0 or Dukes’ type B or C
- 1830 • Pre- or postoperative chemotherapy and/or radiation therapy allowed.

1831 *Exclusion criteria*

- 1832 • Clinical diagnosis of HNPCC or FAP
- 1833 • Local resection for colorectal cancer (e.g., TEM procedure)
- 1834 • Life expectancy less than 2 years due to concurrent disease (e.g., cardiac disease, terminal
1835 multiple sclerosis, liver cirrhosis)
- 1836 • Inability to provide informed consent or refusal to do so.
- 1837 • Inability to comply with the control or intense follow-up programme.
- 1838 • Participation in other clinical trials interfering with the follow-up programmes

1839

1840 *Informed consent* (written) will be obtained within 30 days after surgery and after the primary tumor
1841 classification has been made. Patients refusing to participate will be asked for consent to be
1842 followed in an observational analysis, using data on their actual follow-up program and their clinical

1843 course.

1844

1845 *Randomisation and treatments*

1846 Randomisation will take place by telephone, E-mail (or FAX) from a central randomisation unit
1847 located in the offices of the Cochrane Colorectal Cancer Group. Randomisation will be stratified
1848 according to tumor stage and clinical centre. Randomisation will be blocked, in variable groups of 4
1849 or 6. The allocation procedure will be concealed to participating care providers.

1850

1851 *Study Follow-up Regimens*

1852 CEA will be measured on all colorectal cancer patients before surgery or preoperative adjuvant
1853 therapy and after the completion of primary treatment. All patients will have a “clean colon” within 3
1854 months perioperatively, and at least one perioperative imaging procedure (Ultrasound, MR, or CT)
1855 of the liver and x-ray of the lungs. In both study groups an unlimited number of endoscopies will be
1856 allowed. Interval diagnostic evaluation also will be allowed for all subjects presenting symptoms.

1857

1858 1. *Low-volume follow-up regimen*

- 1859 • CEA, multislice CT/ or MRI of the liver and X-ray or CT of the lungs one year after
1860 surgery. For rectal cancer with re-established luminal continuity, an MR scan of the
1861 pelvis and/or endorectal ultrasound (by a dedicated sonographer) at 6, 12, 18, 24, and
1862 36 months after surgery. For patients with abdominoperineal resection, an MR scan of
1863 the pelvis at the same intervals.
- 1864 • Patients will be instructed to contact their recruitment centre if symptoms of recurrence
1865 occur.
- 1866 • If recurrent disease is suspected, diagnostic measures and treatment used normally in
1867 the individual centre will be applied.

1868 2. *High-volume follow-up regimen*

- 1869 • CEA, multislice hepatic CT or MR and/or PET scans at 6, 12, 18, 24, and 36 months.
1870 For rectal cancer with re-established luminal continuity, MR scan of the pelvis and/or
1871 endorectal ultrasound (by a dedicated sonographer) at 6, 12, 18, 24, and 36 months
1872 after surgery. Biopsies should be taken if suspected areas are found. For patients with
1873 abdominoperineal resection, MR scan of the pelvis at same intervals.
- 1874 • Patients will be instructed to contact their reference centre if symptoms of recurrence
1875 occur.
- 1876 • If recurrent disease is suspected, diagnostic measures and treatment used normally in
1877 the individual centre will be applied.

1878

1879 *Data to be obtained:* the following data will be obtained on all randomised subjects and those who
1880 give consent for observational study:

- 1881 • Baseline demographic, clinical, and lifestyle factors (date of birth, major chronic
1882 illnesses, smoking, alcohol intake, medications, etc).
- 1883 • Results of all diagnostic evaluations for metastatic disease during the initial
1884 evaluation
- 1885 • Detailed description of initial surgical, adjuvant, and radiation treatment
- 1886 • Findings from all cancer surveillance tests obtained after diagnosis
- 1887 • Detailed description of all cancer treatments administered after randomisation
- 1888 • Quality of life (QOL) assessment by telephone interview at 1, 3 and 5 years after
1889 randomisation. A standardised and validated QOL instrument, that takes follow-up
1890 regimens into consideration, will be used.

1891

1892 *Statistical analysis and power*

1893 The primary effect parameter of the study will be total mortality and cancer-specific mortality after 5
1894 years; the secondary endpoint will be time to diagnosis of recurrence (*i.e.*, recurrence-free survival)
1895 and quality of life.

1896 Results will be evaluated both on an intention-to-treat basis and on an as-treated (per protocol)
1897 basis. Patients who withdraw their informed consent and thus change their follow-up programme
1898 will remain in their allocation group in evaluations conducted on an intention-to-treat basis, and will
1899 be excluded in evaluations conducted on a per-protocol basis.

1900 Non-randomised patients and patients who withdraw their informed consent will be analysed
1901 separately.

1902 On the basis of the results listed in Figure 1 in the protocol, an estimate of 5 years' mortality at
1903 60% and a MIREDIF (Minimal Relevant Difference) of 6% seem justified. With a risk of type 1 error
1904 at 5% and type 2 error of 15%, about 1,100 patients should be randomised to each group. With an
1905 expected dropout rate of about 20%, the planned number of randomised patients should be 2,500.

1906 Survival data will be analysed according to the Kaplan-Meier method. Comparisons between
1907 groups will be made using the log-rank method. Binominal data will be analysed with Chi-square
1908 statistics and continuous data will be analysed with the Mann-Whitney U test.

1909 Level of significance = 5%.

1910